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EVIDENCE FOR NORMAL SEGREGATION OF SPECIES-SPECIFIC ANTIGENS IN THE BACKCROSS OF SPECIES HYBRIDS IN DOVES[1]

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Received May 17, 1945

THE segregation in backcross generations of antigenic characters of the red blood cells, specific to one species as contrasted with another, has been reported from this laboratory for several species crosses of pigeons and doves. Probably the majority of the cellular antigens particular to Pearlneck (*Streptopelia chinensis*) as compared with Ring dove (*St. risoria*), and of *Columba guinea* as compared to *Columba livia domestica*, have been obtained in unit form as a result of such segregation in the backcross population (IRWIN et al. 1936; IRWIN 1939). A comparable separation of the antigenic components of the cells would be expected in the backcross progeny of the species hybrids from any two species of animals which produce fertile hybrids.

A third species, Senegal (*St. senegalensis*), has been shown to share with Pearlneck all of some and part of other unit-antigens which distinguish Pearlneck from Ring dove (IRWIN and COLE 1940). Hence if the antigens peculiar to Senegal, as compared to those of Ring dove, could also be obtained as units, there would be possible a reciprocal comparison of the unit antigens of Pearlneck and Senegal, respectively, which would be of special interest from the point of view of the relationship of these two species. The studies to be presented in this paper represent the first steps in the process of obtaining the cellular components of Senegal as units.

MATERIALS AND METHODS

Several hybrids from the cross of Senegals and Ring doves were mated to Ring doves. Although offspring were occasionally obtained from the female hybrids, more backcross progeny resulted from the use of hybrid males. Four such backcross families—D608, D612, D784 and D809—were produced from the matings of hybrid males D376A_2, V, L, and M, respectively. Other backcross families with a smaller number of offspring were obtained in other matings, but the reactions of the cells of these hybrids are not included in this report. The matings were under the general supervision of L.J.C.; the immunological part was done by M.R.I.

Except that Senegal antiserum was used in the present studies, the details of the technics employed in determining the segregation of specific Senegal

[1] Paper No. 347 from the Department of Genetics, UNIVERSITY OF WISCONSIN. These experiments have been supported in part by grants from THE ROCKEFELLER FOUNDATION and from the WISCONSIN ALUMNI RESEARCH FOUNDATION.

[2] Grateful acknowledgment is made of assistance in the laboratory phases of these investigations by DRS. C. D. GORDON, ALFRED GOLDEN, and JOHN R. DICK. DRS. GEORGE W. WOOLLEY and N. L. CUTHBERT also aided in the production of the backcross hybrids.

characters in this report parallel those given in an earlier paper (IRWIN and COLE 1936), which dealt with the segregation of antigens peculiar to Pearlneck in the first backcross generation following the cross of Pearlneck and Ring dove. The presence or absence of the agglutination reactions given in table 1 were usually tested microscopically. If the absorbing cells (that is, those of Ring dove and the individual hybrid) were distributed at random when observed at low-power magnification, the absorption was regarded as being complete. Hence the cells of any other individuals which showed definite clumping with such a reagent were considered to have at least one antigen other than was present in the absorbing cells.

EXPERIMENTAL RESULTS

When a Senegal antiserum (produced in a rabbit) is absorbed by the cells of Ring dove, the antibodies remaining in the antiserum are those which are specific for the respective cellular antigens of Senegal. If, however, the absorption is done by a combination of cells of Ring dove and any individual of the first backcross generation ("quarter-Senegal" or $\frac{1}{4}$ Senegal-$\frac{3}{4}$ Ring dove), not only are the antibodies removed for the antigens shared by Senegal and Ring dove, but also those for which antigens are present in the backcross hybrid. For example, if Senegal cells have ten antigens (as A to J, inclusive) which set it apart from Ring dove, and a backcross bird has six (E through J) of these, the "reagent" prepared by the use of its cells in absorption would contain antibodies for only four antigens (A, B, C, and D). Any reactions of this reagent with the cells of other backcross birds would be by virtue of the presence of antigens A, B, C, or D, singly or in combination. This hypothetical explanation is in line with current belief and experimental findings on the specificity of antibodies and antigens.

It has been shown (IRWIN and COLE 1945) that the conclusion is inescapable that individual Senegals may differ in antigens peculiar to the species, as compared with Ring dove. Should there likewise be individual differences in Ring dove in antigenic content of substances *common* to it and Senegal, the reagents for the specific characters of Senegal would vary, depending upon the antigenic content of the Ring doves used in the absorptions. Fortunately, no such differences among Ring doves in their relationship to Senegal (or Pearlneck) have been noted up to the present. Except when attempting to discover whether such individuality exists within Ring doves, the usual laboratory procedure has been to pool the cells of many individuals for use in agglutinin absorption. This procedure would tend to mask individual differences in the absorbing cells, if any were present.

As previously reported, some differences in antigens have already been shown among the species hybrids between Senegal and Ring dove (IRWIN and COLE 1945). Hence any cellular substances present in one hybrid and not in another could account in part for differences between families of the respective backcross offspring, and also for a part of the differences encountered within a backcross family. That is, D376L (parent of family D784) possessed

TABLE 1

Segregation of cellular antigens specific to Senegal in individuals of the first backcross generation.

CELLS		REACTIONS WITH THE CELLS OF HYBRIDS OF THE FIRST BACKCROSS GENERATION																
		D608																
	(R.D.)	L	Q	R	W	A_2	D_2	R_3	X_2	B_2	P_3	A	H	L	P	R	T	V
Ring dove	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Senegal	8	6	7	7	8	7	9	7	7,8	7	6,7	6,8	6,7	6,7	6,7	6,7	6,7	6,7
D608L	7,8	o	+	+	+	+	C	C	C	+	+	C	+	+	+	+	+	+
D608Q	5,6	o	o,?	+	+	+	C	C	C	+	o	+	o,±	±	+	②	+	±
D608R	5,7	o,+	+	o	o,±	+	+	±	+	+	+	±	+	C	C	+	+	+
D608W	5,7	o	+	+	o	+	+	+	+	+	+	+	+	+	C	+	+	+
$D608A_2$	5,7	o,±	+	+	+	o,?	C	C	C	C	+		+	+	+	+	C	+
$D608D_2$	4	±	+	+	+	C	o											
$D608R_3$	7	o	+	o	o	o		o	+	+	+		+			+	C	+
$D608X_2$	5	+	+	+	+	+		+	o	+	+	+	+	+	o	+	+	o
$D608B_2$	7	+	+	+	+	+		+	+	o			+					+
$D608P_3$	6,7	+	+	+	+	+			+	+	o	+	+	+	+	+	+	+
D612A	7,8	+	+	+	+	+	+		+	±	+	o	+	C	+	+	+	+
D612H	5,6	+	+	+	+	+	+	+	+	+	②	+	o	o,±	+	+	+	+
D612L	6	o,+	+	C	+	+	+	+	+	+	+	+	+	o	+	+	+	+
D612P	5,6	+	+	+	+	+	+	+	+	+	+	+	+	+	o	+	+	o
D612R	6	o	+	C	+	+	C	+	+	+	o	+	+	+	+	o	+	+
D612T	6,7	o	+	C	+	+	+	+	+	+	o	+	+	o	o,+	+	o	o,±
D612V	6,7	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	o
D612X	5,7	±	±	+	+	+		+	+	+	±	+	o,±	o	+	+	+	+
$D612A_2$	4,7		+	+	+	o,+		+	+	+	+	+	+	+	C	C	C	C
$D612C_2$	7	+	+	+	+	+	+	+				C	C	+	C	+	C	C
$D612H_2$	4,7	o	+	o	o,±	o	+	②	+		+	o	+	C	C	+	+	+
$D612L_2$	5,8	+	C	C	C	C	C	+	+		+	+	+	C	C	+	C	C
$D612C_2$	5,7	+	+	+	+	+		②	+	C	+	+	+	+	+	+	+	+
$D612D_2$	4,7	+	+	+	+	+		+	+	+	+	C	+	+	+	+	+	+
$D612J_2$	4,6	+	+	C	+	+		+	+	+	±	C	+	+	±	+	+	o
$D612L_2$	5	o	+	+	o	+		+	o,±	+	o	+	+	o,±	+	+	o,+	o
$D612M_2$	5,8	+	+	+	+	+		+	+	+	+	+	+	+	C	+	+	+
$D612V_2$		+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+
D784D	6	±	+	+	+	+		+	+	+	±	+	+	+	+	+	+	+
D784E	7,8	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+
D784F	7,8	+	+	C	C	+		C	C	C	+	C	C	C	C	+	+	C
D784G	6,7	+	+	C	C	+		C	C	C	+	+	C	C	C	+	C	C
D784J	2,5	+	+	+	+	+			+		o,+	+	+	+	+	+	+	+
D784K	2,3	+	+	+	o,+	+			+		o,+	o,+	+	+	+	+	+	+
D784L	5,6	+	+	+	+	+		+	+	+	+	+	+	±	+	+	+	+
D784M	6	+	+	+	+	+		+	C	②	+	+	+	+	+	+	C	+
D784N	2,4								±		o							
D784R	4								+		o							
D784T		+	+	+	+	+			+		+	+	+	+	+	+	+	+
D784U		+	+	C	+	+			+		±	+	+	+	o	+	+	o
D809B	7,8		C	C	C	C				C	+	C	C	C	C	C	C	C
D809C	6	+	+	C	C	+			+	C	+	C	+	+	+	+	+	+
D809D	5,6	+	+	+	+	+			+	+	C	+	C	+		+	+	+
D809F	7	+	+	+	+	+			+	+	+	±	+	C		+	+	+
D809K	5	+	+	+	+	+			o	+	+	+	+	+	?	+	+	o
D809L	7,8	±	+	+	+	C			+		+	+	C	+		C	+	+

. Symbols: "C" indicates complete agglutination; a "+"=strong agglutination; a "±"=definite but weak agglutination; a "?"=doubtf
agglutination was visible microscopically. If 1=90, 2=180, 3=360 . . . 8=11,520.

ENERATION, USING SENEGAL ANTISERUM FIRST ABSORBED WITH RING DOVE CELLS AND THEN WITH THOSE OF THE RESPECTIVE

D612 | D78

V	X	A_3	C_2	H_2	L_2	C_3	D_3	J_3	L_4	M_3	V_3	D	E	F	G	J	K
o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
6,7	7	6	6	6,7	7	4,5	4,5	6,7	7	3,4	7	6,7	5,7	4,5	6,7	3,8	7,8
+	+	+		+	+	+	+	+	+	±	+	+	+	+	+	+	+
±	+	②		+	o,±	o	o,±	+	+	o	±	±	o	+	+	+	+
+	C	②		+	+	o	o	+	+	o	+	+	o	+	+	+	+
+	+	+		+	+	+	o,±	+	+		+	+	+	+	+	C	+
+	+	+		+	±	∪	o,±	+	+		+	+	o	?		C	+
+	+			±				+	+							C	+
o	+	+		+	+	+	+	o	+	+	o	+	+	+	+	+	+
+				+					+							C	+
+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+
+	C	+	+	+	?,+	±	+	+	+	+	+	+	+	+	+	+	+
+	+	o,+	+	+	o,+	±	+	+	+	±	±	+	+	±	+	+	+
+	+	+	+	+	o,+	+	+	+	+	o	±	+	+	+	+	+	+
o	+	+	+	+	+	+	+	o	+	+	±	±	+	+	+	+	+
+	+	+	o	+	+	+	±	±	+	o	+	+	+	+	C	+	+
o,±	+	+	o	+	o,+	+	?	?	+	o	±	②	o,+	+	C	+	+
o	+	+	+	+	±	+	+	±	+	+	+	+	+	+	+	+	+
+	o	o	+	C	o	o,±	+	+	+	o	o	+	+	②	+	+	+
C	+	o,±	+	+	±	±	+	+	+	+	+	+	+	+	+	+	+
C	C	+	o	C	+												
+	+	o	o	o	o,±	o	o	+	+	o	+	+	o		+	+	+
C	+		+	+	o,±	+	+	+	+	±	+	+	+	+	+	+	+
+	+	±		+	±	o,?	+	+	+	o	+	+	o	+	+	+	+
+	+	+		+	+	+	o	+	+	+	+	C	+	+	+	+	+
o	+	+		+	+	+	+	o,?	+	+	±	+	+	+	+	+	+
o	+	+		+	o	±	o	o	o	o	±	+	+	+	+	+	+
+	C	+		+	+	+	+	+	+	o,±	+	+	+	+	+	+	+
+	+	+		+	+	+	+	?	+	+	o	+	+	+	+	C	C
+	+	+		+	+	+	+	+	+	+	+	o	+	o	+	+	+
+	+	+		+	o	+	②	+	+	②	+	+	o,±	+	+	+	+
C	C	+		C	+	+	C	C	+	+	+	+	+	o,±	+	+	+
C	C	+		C	+	C	C	C	+	+	C	+	+	②	o	+	+
+	+	+		C	+	+	+	+	+	+	+	+	+	②	o	o	+
+	+	+		+	+	+	+	+	+	+	+	+	o	②	o	o	o
+	+	o		C	②	+	+	+	+	+	+	+	o	±,+	+	+	+
+	+	o		+	②	±	+	+	+	±	+	+	+	±	②,?	+	+
									+			+	②	②	o	o,±	o,±
									C			+	⑤	②	?	o,±	+
+	C	+		C	+	+	+	C	+,C	+	+	+	+	+	+	+	+
o	+	o		C		+	+	o	+		±		+	+		+	+
C	C	+			+			C	+			+	+	+	+	+	+
+	+	+		C	+	+		+	+			+	+	±	+	+	+
+	+	+		+	+	+	+	+	+			+	+	+	+	+	+
+	+	+		+	±	+	+	+	+	±		+	+	+	+	+	+
o	C	+		+		+	+	o,+	+			+	+	+	+	+	+
+	+	+		C	±	+	o	+	C			+	+	+	+	+	+

doubtful reaction; a "o" = no agglutination at the first or absorbing dilution (1:90) of the antiserum. A "②" indicates no rea

NG DOVE CELLS AND THEN WITH THOSE OF THE RESPECTIVE INDIVIDUALS AS GIVEN.

		D784												D809						
M_2	V_2	D	E	F	G	J	K	L	M	N	R	T	U	B	C	D	F	K	L	CELLS
o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	Ring dove
3, 4	7	6, 7	5, 7	4, 5	6, 7	3, 8	7, 8	6, 7	6, 7	7, 8	6	6	7, 8	5	7	7	6	7	5	Senegal
±	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	D608L
o	±	±	o	+	+	+	+	o	+	+	±	?, +	o, +		+	+	+	+	o	D608Q
o	+	+	o	+	+	+	+	+	+	+	+	+	+		+	+	o	+	o	D608R
	+	+	+	+	+	C	+	+	±	+	C	+	+		+	+	o	+	o	D608W
	+	+	o	?		C	+	+	+	+	+	+	+		+	+	+	+	+	D608A₁
																				D608D₁
						C	+			+	+		+							D608R₁
+	o	+	+	+	+	+	+	+	+	+	+	+	+		+	o, +	+	o	±	D608X₂
						C	+			+	+		+							D608B₂
+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	D608P₂
+	+	+	+	+	+	+	+	±	+	+	+	+	+	+	+	+	+	+	+	D612A
±	±	+	+	±	+	+	+	+	+	+	±	+	②	②	±	+	+	+	+	D612H
o	±	+	+	+	+	+	+	+	+	+	+	+	+	+	±	C	C	+	±	D612L
+	±	±	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	±	D612P
o	+	+	+	+	C	+	+	+	+	+	±	+	+	+	+	+	+	+	±	D612R
o	±	②	o, +	+	C	+	+	+	+	+	±	+	+	+	o	+	+	+	o	D612T
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	D612V
o	o	+	+	②	+	+	+	+	+	+	+	±	±	②	o	+	+	+	±	D612X
+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	C	+	+	+	D612A₂
																				D612C₂
o	+	+	o		+	+	+	+	+	+	±	+	+		+	+	+	+	o	D612H₂
±	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	D612L₂
o	+	+	o	+	+	+	+	+	+	+	C	+	+		+	+	+	+	±	D612C₂
+	+	C	+	+	+	+	+	+	+			+	+		+	+	+	+	±	D612D₂
+	±	+	+	+	+	+	+	+	+			+	+		+	+	+	+	±	D612J₂
o	±	+	+	+	+	+	+	+	+	+	+	+	+		o	o	o	o	o	D612L₂
o, ±	+	+	+	+	+	+	+	+	+			+	+			+	+	+	+	D612M₂
+	o	+	+	+	+	C	C	+	+	+	+	+	+		+	+	+	+	+	D612V₂
+	+	o	+	o	+	+	+	+	+	+	±	o	+	②	?	+	+	+	+	D784D
②	+	+	o, ±	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	±	D784E
+	+	+	+	o, ±	+	+	+	+	+	+	+	+	+	±	+	+	+	+	+	D784F
+	C	+	+	②	o	+	+	+	+	+	+	+	+	②	+	+	+	+	+	D784G
+	+	+	+	②	o	o	+	+	+	+	o	+	+	②	o	o, +	+	+	+	D784J
+	+	+	o	②	o	o	o	o, ±	±	±	o	+	+	②	o	o, +	o	+	±	D784K
+	+	+	o	±, +	+	+	+	o	o, +	+	o, +	+	+	②	+	o, +	+	+	+	D784L
±	+	+	+	±	②, ?	+	+	+	o, ±	+	+	+	+	②	+	+	+	+	+	D784M
		+	②	②	o	o, ±	o, ±	o	o	o	o, ±	+	+	②	?	o	o	o, ±	o	D784N
		+	②	②	?	o, ±	+	±	+	+	o	+	+	②	②	±	±	+	±	D784R
+	+	+	+	+	+	+	+	+	+			o	+		+	+	+	+	+	D784T
	±		+	+		+	+	o	+			+	o, ±		+	+	C	+	±	D784U
		+	+	+	+	+	+	+	+	+	+		+	o, ±	+	+	+	+	+	D809B
		+	+	±	+	+	+	+	+	+	+	+	+	+	o	+	+	+	±	D809C
		+	+	+	+	+	+	+	+	+	+	+	+	+	+	o	±	+	±	D809D
±		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	o, ±	+	+	D809F
		+	+	+	+	+	+	+	+	+	+	+	+	+	+	o	±	o	+	D809K
		+	+	+	+	+	+	+	+	+	+	+	C	+	+	+	+	+	o	D809L

1 dilution (1:90) of the antiserum. A "②" indicates no reaction at the second dilution (1:180). The digits represent the highest dilution of the reagents at which

probably all of the d-2 character of Pearlneck (IRWIN 1939) which is found in Senegal, and also of d-4; D376M possessed d-1 in addition to d-2 and d-4, as did both D376V and A_2, but these two birds were probably not identical in antigenic composition, and each differed in that respect from D376M. It would not be expected that d-1 would appear in any backcross progeny of D376L, whereas d-1, d-2 and d-4 would segregate in the backcross families of the three other hybrids.

At the time these backcross offspring were being produced, only one or two of the nine or ten unit-antigens of Pearlneck were recognized as single entities. Hence it was not possible to assay the various backcross individuals for the presence or absence of a part or all of these cellular characters in each. Rather was it necessary to compare the antigens of each backcross individual with those of as many others as was possible. The results obtained in such comparisons were guides as to which birds of the first backcross generation should be used in further backcrosses. The reactions of the cells of the backcross birds in these four families, with the reagents prepared by their use with Ring dove cells in absorptions of Senegal antiserums, are given in table 1.

It will be noted in the table that the majority of the reagents (Senegal antiserum absorbed by a combination of the cells of Ring dove and those of a backcross hybrid) were tested with most of the cells of the table. These tests were necessarily spread over a period of nearly two years. The number of different cells which could be tested at any time by a particular reagent depended upon the quantity of cells for absorption which could be obtained from a hybrid at each bleeding. Usually about 0.8 to 1.5 cc of cells were obtained from each bird, and this provided about an equal volume, or slightly less, of a reagent. The cells of about 10 or 12 different birds could ordinarily be tested with a single reagent at any one time.

Probably somewhat over half of the combinations of cells and reagents listed in the table were made twice or more often, with duplication of the presence or absence of agglutination in nearly all instances. A few discrepancies were observed, however, and are so noted in the table. That is, definite clumping at one time as compared with no clumping at another in our opinion represents a discrepancy, whereas differences in degree of the reaction do not. Some of the discrepancies were probably due to differences in antibody content of the different Senegal antiserums used in these tests, and a smaller proportion to differences in reactivity of the same serum at different times. Also, the errors inherent in laboratory technic undoubtedly accounted for still others. The recorded discrepancies, however, are relatively few and do not detract from the general conclusion to be drawn of a segregation within these backcross families of cellular antigens specific to Senegal.

The highest dilutions at which the reagent for Senegal-specific substances reacted with the cells of these backcrossed hybrids are given in the second column of the table. Since the first dilution of the mixture of reagent and cells was at 1:90, and the dilutions were doubled at each step, 2 = 180, 3 = 360 · · · 8 = 11,520. The cells giving reactions at the lowest dilutions were D608D_2 at the

fourth dilution, or 1:720, D784K, at either 1:180 or 1:360, and D784N, at 1:180 and 1:720. The cells of other birds were intermediate in quantitative reactions; some were approximately equal to those of Senegal—that is, at the eighth dilution. But it will be noted that the cells which had reacted at the same dilution of the reagent as Senegal cells—as D608L, D612A, L_2 and M_3, and others—did not by absorption remove all the antibodies for Senegal cells (see second line of data of the table). That is, no backcross hybrid contained all the antigens present in the cells of the various Senegals used in these tests. In fact, it is probable that none of these backcross hybrids contained all the antigens of its hybrid parent, although not all the tests necessary to determine this point were made.

Assuming that Senegal differs from Ring dove in about the same number of specific antigens as does Pearlneck (that is, nine or more), one can calculate the chances that backcross individuals would contain either all the specific antigens of the hybrid parent, or none. For this estimation, random assortment of the chromosomes bearing the causative genes is assumed. If there were nine such substances, each produced by one or more genes on nine chromosomes, the chances of any individual taken at random having either all the antigens of its hybrid parent, or none of them, would be $1/2^n$; since $n=9$, this would be one chance in 512. It is not surprising, then, that no bird of either kind has been observed among the 70-odd tested to date of the first backcross generation.

It will be noted in the table that the absorption with the cells of D608L removed completely antibodies not only for itself but for those of D608Q, W and R_2, as well as for the cells of four individuals in the D612 family (D612R, T, H_2 and L_3). The interactions of the reagents and cells of these eight birds offer one means of estimating the minimum number of antigens which are segregating in the backcross progeny. The cells of D608L will then definitely have all the antigens found in these seven birds. The cells of D608Q removed antibodies only for themselves, as also did those of D612R, T, H_3, and L_3. Assuming that the differences between the corpuscles of these four birds were due to but one antigen in each, one could tentatively assign antigen **A** to D608Q, **B** to D612R, **C** to D612T, **D** to D612H_2 and **E** to D612L_3. Since the cells of D608R_2 absorb antibodies for D612H_2, they presumably contain antigen **D**, plus one other (**F**) as the cells of D608R_2 are agglutinated by the reagent of D612H_2. The reagent of D608W failed to agglutinate the cells of D608R_2 with antigens **DF** (that is, antibodies for the **DF** antigens of D608R_2 were absorbed by D608W), and despite the discrepant reactions with those of D612H_3, an additional antigen (**G**) must be proposed for D608W, making it **DFG**. And because D608L has at least one component (**H**) more than D608W, its antigenic formula would be **ABCDEFGH**, as a minimum. The cells of the hybrid parent were agglutinated by the reagent of D608L, requiring the assumption of still an additional component in the cells of the hybrid parent. Hence it is safe to conclude that undoubtedly nine or more cellular substances are segregating in these backcross individuals. In view of the close relationship of the unit-

antigens of Pearlneck to Senegal (IRWIN and COLE 1940), one would expect to find about the same number in Senegal as are peculiar to Pearlneck in contrast to Ring dove. However, whether the unit characters of Pearlneck are also units in Senegal is an open question.

It is unfortunate that cytological studies of the chromosomes of birds in general are as yet so difficult; otherwise the species hybrids possible in pigeons and doves would offer excellent material in animals for cytological analysis. The difficulties encountered in such studies in birds have been given by PAINTER and COLE (1943). However, despite the lack of a cytological examination of synapsis in the hybrids between Senegal and Ring dove, some information may be gained from an analysis of the distribution in the first backcross generation of cellular substances specific to Senegal. For a discussion of various kinds of chromosome behavior in species hybrids in plants and animals, principally in insects, and references to pertinent papers, the reader is referred among others to review papers by FEDERLEY (1932) and by SAX (1935).

Obviously, any information to be obtained as to the assortment of the chromosomes of these two species, by an examination of this backcross population, may be deduced only from the distribution of the antigenic characters. Only by inference can any light be shed on the behavior of the chromosomes, carrying the causative genes of these antigens. It would be reasonable to expect normal synapsis, with subsequent random assortment, within the species and backcross hybrids of those chromosomes derived from the parental species which carry genes affecting only the cellular substances common to the two species. (Were there aberrations of such chromosomes in either or both species, it is probable that these could not be detected at present, although, of course, synapsis would not be expected to be normal in such cases. But since no information on this point is available, it will not be considered further here.) It would seem, then, that irregularity of chromosome distribution would be expected to occur primarily, if at all, among the chromosomes which carry one or more genes producing species-specific effects of the blood cells.

Evidence has already been presented that there are probably nine or more antigens of Senegal which distinguish it from Ring dove. It is probable, but not at all certain, that these nine antigens are produced by a gene or genes on an equal number of chromosomes of Senegal. (Whether any or all the genes on these chromosomes of Senegal are linked with others which produced substances shared by the two species is a possibility, but still an unanswered question.) If this assumption be granted, and if assortment of these nine chromosomes in the species hybrids be at random, there would be expected a minimum of 512 different combinations of the nine antigens, including the absence of all. It is therefore extremely unlikely that, on the basis of chance alone, any combination of antigens would be repeated often in the small number of backcross birds listed in the table. Also, since there were antigenic differences among the species hybrids used in the backcrosses, such differences would naturally be passed on to some of the offspring. This must be kept in mind in comparing birds of different families. For example, since D376L, the hybrid

parent of family D784, lacked d-1 in its corpuscles, any backcross hybrid with d-1 from families D612 and D809 would be different from any bird of family D784.

One way of examining the interactions given in table 1 is to examine the cells of all the backcross individuals as to their relative standing in the number of antigens possessed. This can be done, first by enumerating the number of individuals for whose corpuscles the cells of a given bird removed antibodies by absorption—that is, the number of "O" reactions of a particular reagent in the table. For example, the cells of D608L by absorption of Senegal antiserum removed antibodies for the cells of seven other hybrids (608Q, W, R_2, D612R, T, H_2, and L_3) as well as for itself. Those of D608Q removed antibodies only for itself, those of D608R exhausted the serum of antibodies for two others (D608R_2 and D612H_2), of D608W for three (D608R_2, probably D612H_2, and L_3), etc. If these reactions are summarized, there are eight birds (D608Q, D612H, T, X, H_2, L_3, D784K, and N) whose cells removed antibodies only for their own cells, nine (D608X_2, B_3, D612A, R, D784D, J, M, T and U) which removed the antibodies for their own cells plus one other individual, seven (D608R, A_2, probably R_2, D612L, V_3, D784R, D809K) for two others, five (probably D608W and D612P, C_2, D784L, D809D) for three others, two (D612C_3, D784G) for four others, two (D612L_2, D809F) for five others, three (D612V, D_3, and J_3) for six others, five (D608L, P_3, D612A_2, D784F, and D809L) for seven others, probably one (D809C) for eight others, one (D784E) for nine others, and two (D612M_3 and D809B) for ten others. The reagent of one bird (D608D_2) was used very little in the tests and is not included in this summary. Also, if each reagent had been tested with all other cells, the above figures might be changed.

Secondly, the reciprocal relationships of the antigenic content may be tested by determining for the cells of each individual the number of reagents with which its cells gave no clumping. That is, in how many individuals are the antigens of each hybrid wholly contained. It may be noted that, although the cells of D608L by absorptions removed the reactions for seven others, the antigens of this bird were not wholly possessed by any other hybrid. It is, of course, highly probable that the cells of many other birds contained one or more of the probable eight antigens of Senegal which were proposed earlier for D608L.

There were 17 hybrids (D608L, possibly D_2, P_3, D612A, V, A_2, C_2, L_2, D_3, M_3, V_3, D784F, T, D809B, C, D, and F) whose cellular antigens were not wholly found in the corpuscles of any other backcross bird; four (D612L, J_3, D784G, and D809L) whose cellular antigens were wholly found in but one other hybrid—but not a single hybrid—two (D608A_2 and D612P) in each of two other hybrids; four (D608W, D612H, probably D612C_3 and D784E) in each of three others; six (D608R_2 but with only a few tests made, D612R, probably D784D, L, M, and D809K) in each of four others; four (D608X_2, D784J, R, and U) in each of five others; two (D608R and D784K) in each of seven others; two (D612T and X) in each of eight others; one (D608Q) in nine

others; one (D784N) in 11 others; and two ($D612H_2$ and L_3) in each of 13 others. The cells of $D608D_2$ were not tested with more than a very few reagents, and the position of $D608R_2$ in the summary is probably not exact for the same reason. The position of $D608B_3$ is not included in this summary.

If there were any strong tendency for several of the antigens to be distributed other than at random, there should be about an equal number of backcross individuals possessing certain combinations of antigens to those without. Members of either of these two groups would be more or less alike antigenically, particularly if several antigens were involved. No tendency towards grouping of antigens, or the converse, appears in the table. Admittedly the indirect evidence supplied in these data is unsatisfactory for an accurate appraisal of the kind of distribution involved in the backcross. But such evidence as there is suggests that these antigens—and therefore their causative genes—are distributed in a random manner. Also, in so far as the data presented on distribution in the first and second backcross (IRWIN and COLE 1936, 1937) to Ring dove of hybrids between Pearlneck and Ring dove may contribute information, a distribution probably normal of antigens peculiar to Pearlneck was noted there.

If each of the antigens peculiar to Senegal could be recognized singly and appropriate tests for the presence or absence of each were made on the cells of the first backcross population, a very precise answer to the question of random assortment of the species-specific characters would be forthcoming. Although this ideal situation was not realized, it has recently been possible to test the cells of 14 backcross hybrids (including those of three of table 1—namely, D784J, K, and X) for the presence or absence of two unit characters of Pearlneck (d-1 and d-4) which are shared with Senegal (IRWIN and COLE 1940) and two of Senegal. These two antigens of Senegal, tentatively called s-1 and s-8, have fulfilled the same requirements of unit-substances as have been described for the unit-characters of Pearlneck (IRWIN 1939). (The reagents for the respective unit-antigens were prepared by using for immunization of rabbits the cells of backcross birds carrying the antigen in unit form, as d-1. When immune serums so produced are absorbed by Ring dove cells, any antibodies remaining are specific for the particular antigen. The details of such tests will be reported elsewhere.)

These four antigens were distributed among the 14 backcross birds as follows. Antigen d-1 was present in the cells of four birds, absent in those of one, there being only five offspring from a species hybrid ($E153D_2$) which possessed d-1. Similarly, d-4 was found in each of the three progeny (of family D784) from the only species hybrid (D376L) possessing it from which backcross progeny were available. The antigens s-1 and s-8 were present in each of the four species hybrids which were parents of these 14 backcross hybrids. Seven birds contained the s-1 substance, seven did not; six carried s-8, and eight did not. Considering s-1 and s-8 together, there were four birds with both s-1 and s-8, three with s-1 alone, three with s-8 alone, and four with neither. In the five birds whose hybrid parent carried d-1, d-1 appeared once in combi-

nation with s-1.s-8, once with s-1, once with s-8, once in the absence of both, and it itself was absent in the fifth bird when s-1.s-8 were present. Likewise, d-4 was present in one bird with s-1, and in two birds which lacked both s-1 and s-8. These data involve small numbers, but provide no evidence of other than a random distribution of these four antigens in the backcross individuals.

It may be stated that the antigens specific to Senegal appear to be distributed at random in the progeny of the backcross of the hybrid to Ring dove. In addition to this indirect evidence of more or less normal assortment of the nine or more chromosomes bearing the causative genes, there has been no suggestion of a deviation from a distribution according to chance in succeeding backcross progenies. (The data on which this statement is based are even more extensive than those presented in this paper. It is not proposed that these data will be published, but inquiries concerning them will be answered to the best of our ability.) These data cannot be interpreted as indicating that the pairing of the nine or more chromosomes of Senegal with potential partners in Ring dove was completely normal. However, in the light of the present evidence, if there was pairing of such chromosomes in the species hybrids, the synapsis between the respective pairs appeared not to be sufficiently abnormal to be detectable.

On the other hand, there are some data from observations on the sperm of hybrids from another species cross which suggest that the germ plasms of the two species are not entirely compatible. Unfortunately, comparable studies have not been made on the sperm of hybrids between Senegal and Ring dove. SHRIGLEY (1940) reported that the species hybrids between Pearlneck and Ring dove, and many backcross hybrids as well, had a greater proportion of abnormalities of the sperm than was found in either parental species. Further, the backcrossed birds which antigenically more closely resembled the Ring dove possessed fewer abnormalities than did those which resembled the species hybrids. If this is evidence of some incompatibility among the chromosomes in the Pearlneck-Ring dove hybrids, it would appear reasonable to expect a parallel incompatibility among them in the Senegal-Ring dove cross.

SUMMARY

The antigens specific to Senegal, as contrasted to Ring dove, appeared to segregate at random in the first backcross generation; at least the segregation was not sufficiently at variance with expectation according to chance alone to be detected. Because the distribution of these cellular characters of Senegal appeared to be normal, it may be concluded that there was more or less normal assortment in the species hybrid parents of the nine or more chromosomes of Senegal carrying genes for antigens specific to the species. This in turn suggests that there was more or less normal pairing of these nine chromosomes of Senegal with partners in Ring dove.

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ANALYSIS OF A MUTATOR

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INTRODUCTION

SPONTANEOUS mutation is a well known phenomenon. A mutation is considered spontaneous when it cannot be traced back to some agent which is known to influence mutability. The causes of "spontaneous" mutation can be investigated when strains are found which differ noticeably in their inherent mutability.

Recently, high mutation frequency in a strain of *D. pseudoobscura*, race B, was found to be due to a dominant mutator (MAMPELL 1943). During the work on that strain a culture appeared which was characterized by a high number of Minutes and Minute mosaics. This led to the present investigation on a recessive mutator.

The analysis of abnormal mutability offers some difficulties. The phenotype in this case is the mutability found in an individual's offspring, and this phenotype can be safely identified only when the numbers are large; for the frequency of mutant individuals may overlap that characteristic of wild type. The fact that an individual produces no mutation does not necessarily mean that it is wild type with respect to mutation frequency. When an individual does produce a mutation, it may merely be a "normal spontaneous" one. A certain number of mutations in this investigation are probably not induced by the recessive mutator, but no means are available for excluding them. These various factors introduce some inaccuracies which cannot be avoided.

These disadvantages are probably not serious in the present investigation. Hundres of thousands of flies were examined; the individual tests were usually carried out on a large scale and at different times. Furthermore, the mutability induced by this recessive mutator is usually so high, and qualitatively so distinct, that a confusion with normal mutability is hardly possible.

All cultures are the results of pair matings. To avoid confusion with other mutation processes, only Minutes are taken as indicators of the presence of the mutator, since they are typical of the effect produced by this gene.

THE APPEARANCE OF THE PHENOMENON

Most of the cultures produce only Minute mutations. The Minutes seem to include the various kinds of this particular phenotype. It is usually difficult or impossible to distinguish two different Minutes by appearance. Only by locating them can the number of different loci involved be determined; this was not generally attempted. Those which have been located are seen to be distributed over the chromosomes as would be expected (table 1). Because of the similarity between the Minutes it is not known how many mutations account

for a certain number of Minute individuals; if they cannot be told apart by appearance, ten mutants may be the result of one or of ten mutations. But in the case of mosaics, it is known that each mosaic individual is the result of at least one mutation.

There is no doubt that the mosaics represent real mutations, since in some cases they affect the germ line and are then inherited as single factors. About 32 percent of the mosaics are sterile, about 54 percent are fertile but do not have the germ line affected by the mutation; about 14 percent are fertile and transmit the mutant gene for which they are mosaic.

Most notable among other phenotypes which make an occasional appearance

TABLE 1

Distribution of mutations.

X-CHROMOSOME			II CHROMOSOME		
Minute 4	35·5		Smoky	0.0	(50)*
Notch		(26)*	Minute 8		
Minute 17			Minute 14		
Minute 19			Minute 16		
			Minute 18		
			Minute 22		
			Minute 23		
III CHROMOSOME			IV CHROMOSOME		
Minute 5			Minute 3	0.0	
Minute 6			Minute 1		
Minute 7			Minute 2		
Minute 10			Minute 9		
Minute 12			Minute 11		
Minute 15			Minute 13		
Minute 20			Minute 21		

* Numbers in parenthesis refer to number of occurrences.

in the cultures are Smoky and Notch. Both, like the Minutes, may be mosaics as well as whole mutants.

The mutability affects the male and the female offspring equally. The relative numbers of male and female mosaics are so nearly alike that no difference can be assumed.

THE RECESSIVE MUTATOR GENE

From outcrossing flies of the mutating cultures to those of normal cultures (Reedsport) the results summarized in table 2 were obtained. Only the males produce mosaics in their offspring. The number of mosaics produced by the females is negligible when compared to that of the males. In F_2 only a small number appear in either outcross, but in F_3 an appreciable number are obtained from each outcross. Judging by the mosaics, an autosomal recessive gene is here involved. The F_1 males would be heterozygous and therefore show no mosaics in their offspring; one fourth of the F_2 males would be homozygous and give mosaics in their offspring. Although the females do not produce mosaics,

TABLE 2

Result of crossing flies from mutating line to flies from normal line.

	♂ outcross					♀ outcross				
P	+♀♀ from cultures with 0.00% mosaics (0 in 9935)		×	+♂♂ from cultures with 7.65% mosaics (1004 in 13121)		+♀♀ from cultures with 8.83% mosaics (678 in 7680)		×	×♂♂ from cultures with 0.00% mosaics (0 in 7597)	
	% of mos.	% of Min.	mosaics	Minutes	No. of flies	% of mos.	% of Min.	mosaics	Minutes	No. of flies
F_1	3.90	6.53	455	763	11679	0.07	0.53	6	41	7779
F_2	0.02	0.77	2	85	11100	0.16	0.00	7	0	4300
F_3	0.60	0.70	34	40	5683	0.81	0.88	37	40	4573

they transmit the gene. The appearance of the whole Minutes will be discussed later.

In order to assign the recessive mutator to its chromosome a system of crosses was used as shown in table 3. Only those males produce mosaics which

TABLE 3

System of crosses used for locating mutator gene.

"*Sm*" 0.00% (0 mosaics in 714) ♀ × "+" 6.48% (95 mosaics in 1466) ♂

↘

"+" 2.92% (77 mosaics in 2636) ♀ × $\frac{\text{"}Sm\text{"}}{+}$ 5.69% (114 mosaics in 2004) ♂

↓

heterozygous II $\frac{\text{"}Sm\text{"}}{+}$ 0.00% (0 mosaics in 2656)

↓

0.00% mosaics (0), 0.04% Minutes (1) in 2369

"*Sm*" 0.00% (0 mosaics in 906) ♀ × "+" 7.73% (123 mosaics in 1592) ♂

↘

"+" 3.54% (92 mosaics in 2687) ♀ × $\frac{\text{"}Sm\text{"}}{+}$ 4.76% (111 mosaics in 2331) ♂

↓

homozygous II $\frac{\text{"+"}}{+}$ 0.00% (0 mosaics in 2792)

↓

1.33% mosaics (38), 1.12% Minutes (32) in 2864

Flies were taken from cultures with the average mutability indicated in percentage; total numbers are given in parentheses.

are homozygous for chromosome II from the selected line. It was also attempted to locate the gene in chromosome II using Smoky and cinnabar for the crossover test. The mutator is to the right of Smoky, in the vicinity of cinnabar.

THE MOSAICS

Several reasons can be given for the predominance of mosaics. The individuals which have some wild type tissue may survive more often. Most of the gross mutations are lethal to the individual, and they may be detected only when they occur late enough to affect only part of the fly. Thus, dominant lethals are sometimes detected when they happen to be linked to a dominant marker gene and when they arise early in the development of the germ line. On outcrossing such an individual to an unrelated fly the ratio of the dominant to wild type would be upset; such a case has been observed at least once. A male heterozygous for Stubble was outcrossed to a wild type female. There were seven Stubble flies and 358 wild type flies in the offspring; the Stubble flies had tumors and were weak. Sometimes flies emerge with various parts missing. This could be interpreted as the result of the action of dominant lethals arising in somatic tissue and accounting for the missing parts (usually of the thorax, such as legs, wings, and halteres). Obviously, if the dominant lethal occurred somewhat earlier the whole fly would be missing, and the mutation would not be discovered.

Another reason is the greater probability of detection of slight mutants in mosaics. Slight variations in bristle length, are easily overlooked when the entire fly is of mutant phenotype, because these slight mutant types overlap the effects produced by normal variation; when the two kinds of tissue occur in the same fly, however, there is no doubt that a mutation accounts for the difference.

Neither of the above reasons could completely account for the unusually high number of mosaics. There is undoubtedly a more basic cause for their abundance. It is important to know the time at which the mutation responsible for the mosaic has arisen. The mosaic could be the result of mutation in the sperm head after the chromosome has split, or it could be the result of somatic mutation in the zygote or any later stage.

If the mutation leading to the production of the mosaic has arisen in the gamete, the flies would be expected to be approximately bilateral mosaics in the great majority of cases. Although bilateral mosaics are actually observed to be the most frequent ones, it is clear that they are also the easiest to detect.

On the scale at which this work was carried on, involving the examination of hundreds of thousands of flies, it was obviously not feasible to look for mutated patches no larger than one cell. However, there is on record a considerable number of individuals which were mutated for only half the thorax, half the head, or half the abdomen, or for the sternopleural bristles only, or a combination of those or certain other patterns. It is perhaps an adequate approximation to consider the bilateral mosaics the most frequent, the one-quarter mosaics the next most frequent and so forth. On the basis of pattern it is not safe to come to a conclusion about the above alternatives of gamete and somatic mutation, respectively.

In the mutating cultures mosaics for sex linked recessives have been observed. If those are induced by the mutator gene, the mutation cannot have

arisen in the sperm head, but at the earliest in the zygote, since the chromosome concerned is of maternal origin. This, then, is evidence in favor of somatic mutation. Some interesting mosaics will now be described.

Certain Minute mosaics serve as an indication that "deficiencies" of varying extent are produced. When a wild type male was outcrossed to a Stubble female, in two instances, a mosaic occurred in the offspring which was Minute for half the thorax without indication of Stubble, whereas the unmutated half was Stubble. This is interpreted as a deficiency including the Stubble locus, and by removing the gene, it would also remove its phenotypical effect. In a similar case, when a wild type male was outcrossed to a Stubble Hairless^{E} female, a mosaic female in the offspring was Stubble Hairless^{E} on the right side, whereas the mutated left had an abnormal eye and wing, but was wild type for bristles. This probably means that a deficiency arose long enough to include both the Stubble and Hairless^{E} loci, thus removing their phenotypic effects. Similarly, in two instances of an outcross to a Stubble female, there occurred a female one half of which was Stubble, while the other half was wild type for bristles, but had a smaller eye and wing. The latter three cases may also be explained on the same basis as the two following ones—namely haploidy for part of the tissue.

There are two examples for this kind of mosaic. In one case a wild type male was mated to a female homozygous for seven sex-linked mutant genes: *bd^{ct} sct dy rs st se s*. In the progeny, one mosaic was wild type female on one side and *bd^{ct} sct dy rs st se s* female on the other side. Similarly, a *bd^{ct} sct dy rs st se s* male was mated to a female heterozygous for wild type and *bd^{ct} sct dy rs st se s*. In the progeny a mosaic occurred which was wild type female on the right half and *bd^{ct} sct dy rs st se s* female on the left half. Since the side showing the sex-linked recessives was female in both cases, it could not have arisen merely by elimination of an X chromosome, for then, that part would have been male. Although in both cases other explanations are possible, it could both times be a matter of an entire chromosome set being eliminated. Then the part revealing the sex-linked recessives would be completely haploid and, therefore, normal female. In the first case the male set, in the second case the female set could have been the victim. Haploid-diploid mosaics have been described also in *D. melanogaster* where they were first observed (BRIDGES 1925), in *D. miranda-D. pseudoobscura hybrids* (MACKNIGHT 1937), and in *D. pseudoobscura* (CREW and LAMY 1938).

Gynandromorphism also has occurred repeatedly. It could likewise be explained on the basis of an entire chromosome being eliminated. One reason for this might be a mutation of the centromere, its deficiency or inactivation. This would account for both types of observed aneuploidy. Elimination of other chromosomes or chromosome combinations by the same mechanism would probably result in lethality.

Among the above mosaics those involving Stubble and one of those involving the sex-linked recessives show that something happened to the material contributed by the female. This again could have occurred at the earliest in

the zygote; the same is true for the gynandromorphs. If these have been induced by the mutator, it seems likely that the majority of the mosaics is due to somatic mutation. Further evidence for somatic mutation is given in the next section.

ANALYSIS OF MALE AND FEMALE OUTCROSSES

As can be seen in table 2, the F_1 of the male outcross has mosaics and whole Minutes; the F_2 has practically only whole Minutes. If the mutations occur in the F_1 giving rise to the mosaics in that generation, we should expect the germ line to be affected and should obtain whole mutants in F_2. If the F_1 shows no mosaics, as is nearly so in the case of the female outcross, we should expect no whole mutants in F_2. None are observed in that case. It must be emphasized that the whole Minutes in the F_2 of the male outcross do not represent the offspring of F_1 Minute mosaics, but of F_1 wild type flies. This is strong evidence in favor of the mutations responsible for the mosaics arising in the mosaics themselves, and not in the father's gametes.

We have seen that, on outcrossing, a male must be homozygous for the mutator to give mosaics in its offspring. The mutations occur in the F_1 individuals, both male and female, although they are heterozygous. Thus arise the mosaics in F_1 and the whole mutants in F_2. This is the cause of the whole mutants in the F_1 of the female outcross; they represent the residue of the mutation-inducing capacity of the maternal grandfather.

This forces us to a curious conclusion. On the basis of the available evidence we must assume that the mutator gene, when homozygous, is responsible for the production of a factor or factors transmitted through the cytoplasm of the sperm. The F_1 individual, being heterozygous for the mutator, produces the normal wild type counterpart of this cytoplasmic component. And, unless the component should be self-reproducing to some extent, the abnormal component in the F_1 should decrease at least by a factor of two with each cell generation. The bilateral mosaics should be twice as frequent as the one-fourth, the one-fourth twice as frequent as the one-eighth and so forth. The least frequent should be the mutations affecting only one somatic or germ cell, for, by that time, the abnormal component would be too dilute to be very effective.

Now, we must grant the wild type sperm the same right as the mutator sperm; it would transmit the normal component. Therefore, a fly which is homozygous for the mutator, as one-fourth of the F_2 would be, ought not to begin mutating until the normal component is too dilute to be effective. Or, we should here find the reverse of the former case—that is, the bilateral mosaics should be the least frequent and the single cell mutations the most frequent. We notice the lack of an appreciable number of mosaics in F_2. However, the result of germ cell mutations should show and does show in the F_3 of either outcross, even though the mosaics in F_2 were very scarce.

There are two possible reasons for the failure of the females to produce mosaics. It may be assumed that the cytoplasmic component is transmitted through the sperm only. *A priori*, this may seem surprising. But there are such

components as the centriole which are usually transmitted through the sperm, and not through the egg. Furthermore, such components as mitochondria and Golgi bodies may be contributed by the sperm to a larger extent than by the egg. They may also be of quite different appearance or function in sperm and egg, respectively. It is not new to find that an individual's characteristic depends on the genic make up of the female parent; this is known as a maternal effect. As concerns the observable effect on mutability, in this case, the roles are reversed. An individual's mutability depends in fact on the genic make up of the male parent; therefore, this should be called a "paternal effect."

The alternative reason for the lack of mutation in the F_1 of female outcrosses does not contradict the paternal effect which in fact exists. It does contradict the supposition that the sperm contributes a component which is necessarily absent in the egg.

It must first be ascertained whether homozygous females are produced at all and, if so, whether they are fertile. It was found that the mutator is not lethal to the females nor does it sterilize them. There remains one reason for the lack of mutability from the female aside from purely physiological ones. Perhaps the mutator gene can produce its effect only in the presence of a Y chromosome. This would not have to be a specific Y chromosome as is obvious from the fact that the mutability reappears in the F_3 of a female outcross. If the supposition were true, the mutator might show its effect in an XXY female. This has not yet been tested. In this argument it is assumed that the egg is potentially capable of transmitting the cytoplasmic component.

THE MUTATION RATES

There is a general correlation between the mutation rate of the parent cultures and the rate of the offspring cultures. The offspring cultures show an increasing number of mutations with an increasing number in the parent cultures, as can be seen in table 4. The parent cultures in the first row are those with between 4.5 and 7.5 percent mosaics, in the second row with between 7.5 and 10.5 percent mosaics, in the third with more than 10.5 percent mosics. Only cultures with at least three previous generations of inbreeding were included. All the pair matings established from these are summarized under "offspring cultures." The average number of flies per culture depends to some extent on the mutability. The higher the mutability the lower is the number of flies in a culture.

With a greater mutability as judged by mosaics we should expect the whole Minutes to rise proportionally. There should be a correlation between the percentage of mosaics of a certain culture and the percentage of Minute flies in the offspring of the individuals from that culture. Table 4 shows this to be the case.

Although there is a positive correlation between the mutation rates of parent and offspring cultures, we see in table 4 that the offspring rate is about one-half that of the parent rate. This can be explained on several grounds. Part of the variation in the cultures, of course, is due to the expected frequency dis-

tribution. The extremes of the distribution would tend to go back to the center.

Only wild type individuals are used for breeding. Thereby, the more mutable ones are constantly selected against. Furthermore, a gene that has mutated, cannot mutate again (where we are dealing with deficiencies or something corresponding to them). In the absence of selection for it, the phenomenon, in time, would mutate itself out of existence.

The mutation rate may also be influenced by the kind of mating. When a homozygous mutator male is outcrossed to a homozygous wild type female, we should not expect as many mosaics in the offspring as when we cross this male to a heterozygous or homozygous mutator female. In the former case the mosaics would be only the residue of the mutation-inducing capacity of the father. In the latter two crosses mosaics would occur because of that mecha-

TABLE 4

Different levels of mutability.

Parent cultures			Offspring cultures				
% of mosaics	No. of mosaics	No. of flies	mosaics	Minutes	No. of flies	% of mosaics	% of Minutes
6.14	2151	35014	1128	565	30547	3.69	1.88
8.63	2027	23490	667	367	15882	4.20	2.31
13.88	2027	14596	725	281	10642	6.81	2.64

nism as well as from the mutation-inducing capacity of the individuals themselves, for here half the individuals or all the individuals respectively are homozygous for the mutator; they could begin mutating in the zygote, because no wild type component is contributed by the sperm. In the cross of two heterozygotes we supposed that the resulting homozygotes would not mutate at this early stage since the wild type component would prevent this.

Homozygous females may on occasion produce mosaics and thus provide an additional factor for influencing the mutation rate.

But, as can be seen in table 4, the level of mutability tends to be maintained in a certain line. This suggests a further influence on mutability.

When a mutator fly is outcrossed to wild type, the F_1 is not only heterozygous for the mutator, but for the rest of the genes as concerns their mutability. In the mutator strain the flies were constantly selected for high mutation rates. In the wild type strain there was no such selection. We may therefore select for modifying factors. There could also be a different interpretation. The mutation rate may be the result of the activity of the mutator plus the susceptibility to it of the genes to be mutated. That could be the explanation of the different levels of mutability. We can imagine two strains, each homozygous for the mutator, one showing practically no mutations, the other showing

practically 100 percent mutations. This could be accomplished by selecting for or against the genes which are readily influenced by the mutator. There must be many such mutators controlling or influencing the over-all mutation rate of a particular strain, and a certain gene may be susceptible to one but not to another of these mutators. In the various cases of rises in mutation frequency described in the literature the phenomenon soon disappeared. This could be explained by the rapid "acclimatization" of the genic complex. The sudden rise of mutation frequency itself can be explained on the same grounds—namely, when genes are taken out of their normal mutator environment and subjected to a new one by crossing or hybridization, they would undergo a temporary high mutability (STURTEVANT 1939, and others). This suggestion of susceptibility receives support from the following observation.

MUTATION FASHIONS

On the basis of the individual susceptibility of the genes to the mutator, another phenomenon can be explained which has been observed repeatedly in the mutating cultures: mutation fashions. The mutability in different lines may be distinguished qualitatively in some cases. The two main characters which occur in fashions are Smoky and Notch. The predominant phenotype is Minute, and it is the Minute mutations for which the lines were constantly selected. Minute is the commonest mutant phenotype in Drosophila; many loci in different chromosomes are known to produce this effect. But in certain lines there has been a high proportion of Notch or Smoky or certain other mutations. These fashions may persist for some time, and evidently they can be selected for. This is not surprising; in those cases we would select for a susceptible wild type allele of Smoky or of Notch or of a certain other region in preference to the Minute regions. The different kinds of mutability on the basis of our explanation would of necessity have to be qualitative as well as quantitative.

THE IRREGULARITIES

There are several stocks of *Drosophila pseudoobscura* as well as other species which have persistently shown an unexpected number of mutations of the type described here. Although mutability in these strains is nowhere near as high as in the mutator strain, it warrants careful analysis. This is now in progress. The research with these strains has not advanced far enough to allow discussion at this time. But the existence of the phenomenon should be mentioned here, because it would introduce irregularities into the mutator strain. The degree of the irregularities cannot be measured as long as we do not know more about the new phenomenon. The wild type to which the mutator has been usually outcrossed is the Reedsport strain. It has a negligible mutability.

CONCLUSION

There are now enough cases on record to show that the mutability is to a large extent under the control of genes. The evolutionary significance of this fact is obvious. It is also obvious, at least in the present example, that there

must be a carrier between the mutator gene and the genes to be mutated. It is the carrier which arouses our interest in connection with this recessive mutator. Although we cannot exclude any of the cytologically distinct structures, there is no reason to assume that we are dealing with more than a general cytoplasmic component of molecular size. In a study such as this, already full of uncertainty and hypothesis, it is not profitable to extend the discussion.

SUMMARY

A recessive mutator gene in *Drosophila pseudoobscura* is the object of the investigation.

Minutes and Minute mosaics are characteristic mutations in the cultures showing the high mutability.

The mutator is in chromosome II, in the vicinity of cinnabar.

The mosaics represent somatic mutations; when those mutations affect the germ line, they are inherited as single genes.

On outcrossing, only males produce mosaics in their offspring. Possible reasons for the failure of the females to produce the mutations are presented. It is assumed that the mutator when homozygous produces a cytoplasmic component which induces the mutation. The component is transmitted through the cytoplasm of the sperm. This represents a "paternal effect."

The mutation rates resulting from the various possible crosses are discussed. Differential susceptibility of the genes to the mutator may account for the different levels of mutability.

"Mutation fashions" can be explained on the basis of this susceptibility.

It is suggested that the carrier of mutability is evenly distributed through the cytoplasm.

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EVIDENCE OF GENES FOR FEMALE STERILITY IN DAIRY COWS[1]

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SIX different hereditary defects, each conditioned by an autosomal recessive gene, have been reported from the Jersey breeding experiment of the University of California. The two lethals are imperfect epithelium (REGAN, MEAD, and GREGORY 1935) and a recessive type of achondroplasia (GREGORY, MEAD, and REGAN 1942). The non-lethals are cataract (GREGORY, MEAD and REGAN 1943); proportionate dwarfism and flexed pasterns (MEAD, GREGORY, and REGAN 1942, 1943); strabismus (REGAN, MEAD, and GREGORY 1944). Since each of these genes affects the morphology in a specific manner, the afflicted animals can be recognized without difficulty.

This report will present evidence of a specific gene (or genes) conditioning female sterility. As is generally accepted, genes condition character by physiological action. Those that affect morphological expression are readily detected and easily lend themselves to genetic analysis. However, those that condition physiological processes without obvious morphological effects can be detected only by special chemical, biological, or other tests. Genes which condition sterility but which have no obvious morphological effect are likewise difficult to recognize and study.

THE PROBLEM OF FERTILITY AND STERILITY

Fertility and sterility constitute an extensive problem. All degrees from complete sterility to the highest fertility may be encountered. These conditions are determined both by hereditary and by environmental factors. The problem as a whole may depend upon genetics, physiology, pathology, bacteriology, nutrition, and climatology. The study herein reported is limited to females, and only the qualitative phases are considered. It is necessary, therefore, to define the terms fertile and sterile as used in this report. Any cow that has given birth to a calf carried to normal term is regarded as fertile. All quantitative aspects of fertility are disregarded. Any heifer known to be free from infectious diseases such as Brucellosis, but to have failed to produce a calf after repeated services to one or more fertile bulls is classed as sterile. This limitation disregards all cows that develop breeding trouble after one or more births.

All females of breeding ages were classed as fertile or sterile as defined above. Table 1 lists all sterile animals and animals of undetermined fertility.

Heifers of the sterile group need additional explanation. A few never came into heat. Others manifesting regular heat periods, were bred to proved fertile bulls, but either failed to conceive or did not produce a calf. Since each heifer

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TABLE 1

Cows classed as sterile, or of undetermined fertility.

COW	NO. OF MATINGS	SIRE	DAM	DAM'S SIRE	REMARKS
Jerseys					Sterile
419	14	300	306	102785	Kept two years and ten months; died of bloat; sterile
425	8	300D	390	300D	Condemned as sterile
438	5	300D	379	300D	Kept in herd until two years and seven months old; missed several heat periods between matings; sold as sterile
447	5	300D	390	300D	Condemned as sterile
472	8	300C	431	320A	Also ran in pasture with bull for seven months; condemned as sterile
487	10	300D	442	320A	Bred to three different bulls; skipped several heat periods; sold because of breeding trouble
489	7	300D	451	300D	Condemned as sterile
491	11	300D	344	3000	Condemned as sterile
767	9	370A	732	403A	Condemned as sterile
772	13	370A	584	433A	Condemned as sterile
774	5	370A	557	482A	Condemned as sterile
777	12	370A	721	370A	Condemned as sterile
780	6	333C	569	333C	Condemned as sterile
802	9	370A	744	370A	Condemned as sterile
803	9	333C	761	576A	Condemned as sterile; equivalent to a sire-daughter mating of 333C and treated as such in the analysis. Inbreeding coefficient from 333C is 0.406; see figure 1 for pedigree
					Undetermined
340	2	300C	314	116287	Sold because of breeding difficulty
439	4	300D	400	300D	Sold; reacted to tuberculin test
470	7	300D	416	320A	Found dead in pasture six months after last service; may have been pregnant
486	8	300D	403	320A	A t.b. reactor; slaughtered three weeks after last service; probably sterile
565	6	482A	495	300D	Sold because of breeding difficulty. Information incomplete
382	2	300	354	106305	Only calf aborted at 259 days; cow died 18 days later.
827	1	370A	737	333C	Only calf aborted at 224 days; has not conceived again, still in herd
833	1	370A	749	403A	Only calf aborted at 229 days has not conceived again, still in herd
Holsteins					Sterile
1015	2	100B	154	100A	Reproductive organs malformed; condemned as sterile
1031	0	100B	172	100B	Never came in heat; condemned as sterile
1058	3	100B	1039	100B	Condemned as sterile; nymphomania
1061	0	100B	1000	100B	Condemned as sterile; never came in heat
1065	0	100B	1034	100B	Condemned as sterile; never came in heat
					Undetermined
1062	1	100B	1043	100B	Only calf aborted at 227 days; never became pregnant afterwards

that failed to come in heat or to conceive after several services was studied by some member of the Veterinary Science Division of the UNIVERSITY OF CALIFORNIA, the veterinarian's report was often helpful in classifying individual animals. If the veterinarian found that a heifer had abnormal reproductive organs

TABLE 2

Summary of fertile and sterile daughters of all bulls used during the past 25 years.

	OUTCROSSED (f*0–0.03124)				INBRED (f*0.03125–0.469)		
Sires	Fertile	Sterile	Undetermined	f* Range	Fertile	Sterile	Undetermined
Jerseys							
300	12	1[a]	1	—	0	0	0
300A	4	0	0	0.039–0.098	4	0	0
300C	8	0	1[a]	0.0313–0.276	5	1[b]	0
300D	27	2[a]	2[a]	0.132–0.396	9	4[c]	1[c]
320A	15	0	0	0.039–0.345	9	0	0
333C	8	0	0	0.064–0.469	23	2[d]	0
346A	0	0	0	0.297	3	0	0
370A	4	0	0	0.039–0.393	54	5[e]	2[h]
386A	3	0	0	0.138–0.328	9	0	0
403A	0	0	0	0.035–0.169	6	0	0
428A	0	0	0	0.188–0.235	2	0	0
433A	2	0	0	0.102–0.410	11	0	0
482A	0	0	0	0.199–0.445	8	0	1[f]
504A	0	0	0	0.114–0.216	2	0	0
576A	0	0	0	0.338–0.383	2	0	0
3000	11	0	0	0.250	2	0	0
	—	—	—		—	—	—
Total	94	3	4		149	12	4
Incidence of sterility	3.09 percent				7.41 percent		
Holsteins							
100A	3	0	0	0.047–0.325	19	0	0
100B	18	1[a]	0	0.063–0.437	48	4[g]	1
	—	—	—		—	—	—
Total	21	1	0		67	4	1
Incidence of sterility	4.54 percent				5.63 percent		

*f refers to WRIGHT'S coefficient of inbreeding
[a] Inbreeding coefficient 0.0
[b] Inbreeding coefficient 0.0313
[c] Inbreeding coefficients range from 0.264 to 0.396
[d] Inbreeding coefficients range from 0.375 to 0.406
[e] Inbreeding coefficients range from 0.055 to 0.393
[f] Inbreeding coefficient 0.218
[g] Inbreeding coefficients range from 0.250 to 0.406
[h] Inbreeding coefficients range from 0.0469 to 0.1836

and could not reproduce, she was considered sterile and sent to slaughter. Heifers with morphologically normal reproductive tracts, without evidence of pathological changes, required more services before being classified. Some of these heifers were kept to an age of four and one-half years, although most were classified earlier. The average number of services for all Jersey heifers regarded as sterile (including those with abnormal reproductive organs) is approximately nine per heifer. Only a few of the cows remain unclassified (table 2). All these had breeding difficulties of some kind. Some were bred at one or more heat periods, then missed a few periods and died; others contracted a contagious disease requiring removal from the herd; while four aborted and never conceived afterwards.

Because of the arbitrary method of classification, there is a minimum chance for error. All cows listed as fertile are classed correctly. The only chance for error is in the sterile group. The studies of GOWEN (1918) at the Maine Station definitely show that the number of conceptions resulting from the fifth and later services is negligible. The data of ECKLES (1929) from the Minnesota Station are in general agreement with those of GOWEN. The Minnesota cattle, however, have a lower breeding efficiency, and, consequently, there is an appreciable percentage of conceptions resulting from the fifth to the tenth services. Possibly, but not probably, an occasional animal of the sterile group might have produced a calf if kept longer. The nine unclassified heifers were daughters of six different bulls, and only two were produced by sire-daughter matings. Heifers 382, 827, 833, and 1062 may be considered "technically" fertile. None of the unclassified heifers has any effect upon the general or specific conclusions regarding heredity.

MANAGEMENT OF THE EXPERIMENT STATION HERD

The general management of the herd closely conforms to the accepted practices of dairy husbandry for California; MEAD (1942) has described specific management in detail. At all times, a good grade of alfalfa hay and a variety of concentrates are fed in adequate amounts. Up to 1935, pasture was used whenever available; since then the Jersey heifers have had none. Jersey females are bred when their weight reaches about 550 pounds; and Holstein females 750 pounds, regardless of age. Early in the breeding experiment, Jersey heifers were fed so that they calved when about 27 months old. During the past nine years, Jerseys have been forced by more extensive feeding of concentrates, so that they calve at about 22 months. Under the system of forced feeding, they freshen at the same weight as when they calved at 27 months. The schedule of the Holsteins has remained unchanged during the past 25 years.

Throughout the experiment the herd has been tested for Brucellosis; and, except for a few reactors during an outbreak in 1936 and 1937, it has remained free from Brucella infection since 1928. All cows classed as sterile or uncertain reacted negatively to the agglutination test for Brucellosis. The herd has never been infected with Trichomoniasis.

THE HERD RECORDS

The primary object of the breeding experiment was to obtain data concerning the inheritance of milk and fat yields. Since it was foreseen that data could be accumulated that would bear upon other problems of heredity, rather complete records were kept on all animals. The studies of hereditary defects and fertility may be regarded as by-products of the main breeding project.

Breeding services, calvings, abortions, stillbirths, reasons for disposals, and any unusual incidents have always been recorded in detail for each animal in the herd. The data used in this study cover, in brief, the first 25 years of the program. The daughters of all sires used in the herd have been included if old enough to classify. The sires listed in tables 1 and 2 have all been dead one to 17 years.

ANALYSIS OF DATA

The Jerseys include 266 cows, the daughters of 16 bulls; the Holsteins, 94 cows from two bulls. Most of the Jersey sires did not produce enough females for a satisfactory analysis. The number of daughters from one of the Holstein sires, however, permitted a rather complete study. Table 2 summarizes the data. As may be observed, the progeny of the sires are classed as outcrossed or inbred. The degree of inbreeding is determined by WRIGHT's (1923) formula for the coefficient of inbreeding. Any cow having an inbreeding coefficient of less than 0.03125 (the equivalent of one great-grandparent in common) is classed as outcrossed. Any cow whose inbreeding coefficient is 0.03125 or greater is classed as inbred.

The Jerseys

As shown by an inspection of table 2, the incidence of sterility in the inbred Jerseys is more than double the figure for the Jerseys produced by outcrossing. This strongly suggests an hereditary basis.

Bulls 300, 300C, 300D, 333C, and 370A produced enough progeny for a partial if not complete analysis.

With only a few progeny and a minimum number of test matings, the exact relation of the alleles conditioning fertility and sterility cannot well be ascertained. The data at hand, however, permit one to determine the most plausible relation consistent with all the results. Since the sterility involved is found only in females, it is assumed to be sex-limited. With this relation, a pair of alleles (*Aa*) conditioning fertility and sterility might act in a number of ways; but the most plausible relation is as follows:

Genotype	Males	Females
AA	Fertile	Fertile
Aa	Fertile	Fertile
aa	Fertile	Sterile

On the other hand, if one assumes that the *AA* female is sterile and the *aa* fertile, the scheme is essentially the same, the only question being which member of the allelic pair is considered dominant. Dominance has little significance in this case; but since most mutant genes are recessive, one may logically assume that sterility is recessive.

In all the analyses of sire-daughter matings, no distinction was made between daughters resulting from two, three, or four successive generations of the same sire. When 300D was mated to his own daughters, the resulting inbred daughters were classified as eight fertile, four sterile, and one undetermined (table 3)—a good fit if 300D is assumed to be homozygous for female

TABLE 3

Mating results involving sire 300D.

	FERTILE	STERILE	UNDETERMINED
	300D × own daughters		
Observed	8	4	1
Calculated[a]	6	6	
			$\chi^2 = 1.332$
	300D × unrelated cows		
Observed	27	2	2
Calculated[b]	27.55	1.45	
			$\chi^2 = 0.219$
	482A (Son of 300D) × daughters of 300D		
Observed	6	0	1
Calculated[c]	4.5	1.5	
			$\chi^2 = 2.00$

[a] In all these calculations 300D is assumed to be homozygous (*aa*) for female sterility. All his own daughters are assumed to be heterozygous (*Aa*) for sterility.

[b] Here the frequency of the gene (*a*) for female sterility in the unrelated cows is assumed to be 0.05.

[c] 482A and his half sisters are assumed to be heterozygous (*Aa*) for female sterility.

sterility. The unclassified daughter was mated four different times to 300D and was discarded when she reacted to the tuberculin test. She was probably sterile. If one assumes that 300D is heterozygous for female sterility, the fit is poor; the assumption that he is homozygous is therefore justified.

Of the daughters obtained from mating 300D to unrelated cows (table 3), 27 were fertile, two sterile, and two unclassified (numbers 470 and 486 in table 1). Judging from these results, the female sterile gene was present in the unrelated cow population. As might be expected, the frequency of the gene in that population is low; the frequency value is approximately 0.1 or less.

Sire 482A, a son of 300D, was also used. When mated to his paternal half sisters, he produced seven daughters (table 3). This sire and his half sisters are assumed to be heterozygous for the female sterile gene. The results are six fertile, none sterile, and one undetermined—a fair fit even though no sterile

daughters were actually observed. The undetermined daughter was bred at six different heat periods to a proved fertile bull and was discarded because of difficulties in becoming pregnant. She was probably sterile, although she was not condemned by the veterinarian and the number of services is insufficient to classify her as sterile. Even though a sterile daughter was not positively identified among the seven daughters resulting from mating 482A to his paternal half sisters, the results of all three matings make it logical to conclude that 300D is homozygous for a gene that conditions female sterility.

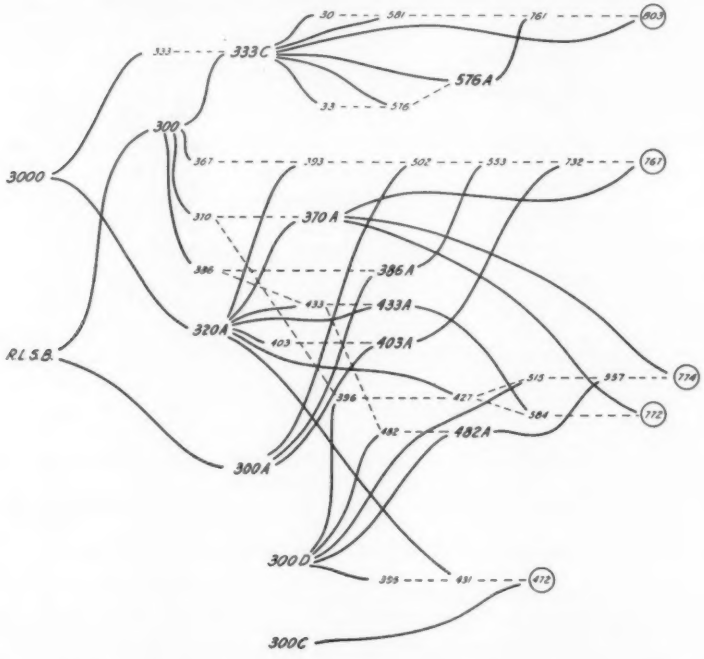

FIGURE 1.—Pedigree net work showing the ancestry of sterile Jersey heifers 472, 767, 772, 774, and 803. Solid lines show sire connections, broken lines dam connections.

Sires 300, 300C, 333C, and 370A, all of which produced one or more sterile females, will now be considered. When sire 300C was mated to unrelated cows, he produced one daughter of undetermined fertility (tables 1 and 2). Bull 300C produced, by sire-daughter matings, three fertile heifers. When he was mated to a great-granddaughter of 300D, the result was a sterile heifer, number 472 (fig. 1). In all likelihood, 300C is heterozygous for the same gene for which 300D is homozygous—a gene that conditions female sterility. It is still possible, however, to attribute the sterility to an environmental cause.

Sire 300, when mated to unrelated cows, produced one sterile and one unclassified daughter. This one sterile daughter is not sufficient to convict him as a carrier of a gene for female sterility. He has a son (333C) and a grandson, (370A), however, both of which transmit female sterility (table 2). Sires 333C and 370A were used extensively in sire-daughter matings, the data from which are summarized in table 4. Judging from the results, sires 333C and 370A are each heterozygous for a gene for female sterility. Presumably, both 333C and 370A obtained the gene for female sterility from sire 300, and only one gene is involved. Absolute proof is lacking, however, since all 13 daughters produced by mating 333C to daughters of 370A or by the reciprocal (370A to daughters of 333C) were fertile.

TABLE 4

An analysis of female sterility for Jersey sires 333C and 370A; results of sire daughter matings.

	FERTILE	STERILE	UNDETERMINED
	333C		
Observed	20	2[b]	0
Calculated[a]	19.25	2.75	
			$\chi^2=0.235$
	370A		
Observed	15	2	0
Calculated[a]	14.9	2.1	
			$\chi^2=0.006$

[a] Calculated on the basis that the sire and half of his daughters are heterozygous for the gene for female sterility.

[b] See remarks on cow 803, table 1.

Three sterile daughters of 370A (767, 772, and 774), only slightly inbred, have not been discussed in detail. Figure 1 shows their ancestry. In considering these animals one should remember that judging from all the tests, sire 320A and his sire (3000) do not carry genes for female sterility and are both presumably homozygous normal. Though the progeny test is incomplete, the limited data available indicate that 300A may not be a carrier. Since, however, he is a paternal half brother of 300, one hesitates to assume, without complete proof, that 300A is homozygous normal. Figure 1 suggests that cow 732 (the dam of sterile cow 767) obtained the gene for female sterility from 300 (as did 370A), though the possibility of 300A's being the donor is not eliminated. The other two sterile daughters are interesting because they involve progenies of both 300 and 300D, sires that introduced female sterility into the herd. As figure 1 shows, 584 (the dam of sterile cow 772) could have obtained the gene for female sterility from either 300 or 300D. Where 557, the dam of the last sterile daughter, 774, obtained the gene cannot be determined. Sire 300D who figures prominently in her pedigree, is apparently homozygous for female sterility. Yet there still remains the more remote possibility that the gene came from 300.

When all matings are considered, it is impossible to determine with absolute assurance whether one or two genes for female sterility are involved in the Jersey herd. Each of the ratios encountered was certainly conditioned by one pair of alleles. There were no adequate genetic tests, however, to prove the relation of the genes for female sterility carried by sires 300D and 300. Despite the likelihood that only one female sterile gene is present, the possibility of there being two has not been eliminated.

The Holsteins

All the daughters of unrelated Holstein sires 100A and 100B are classified in table 2. Sire 100A was used first. None of his daughters produced either by outcrossing or by inbreeding proved to be sterile. Since, however, he produced only two heifers by sire-daughter matings, his genotype for female sterile genes was not determined.

Sire 100B was next used in the herd. His sterile daughters are listed in table 1, and all his daughters are classified in table 2. When mated to unrelated cows, he produced 19 daughters, 18 of which were fertile and one of which (with malformed genital organs) was sterile. This sterile heifer is a granddaughter of 100A (table 1). In the study of a character such as sterility, which may also be caused by environmental factors, one sterile female alone is insufficient evidence to determine the genotype of a parent or grandparent. Hence the status of 100A regarding a female sterile gene was not determined either directly or indirectly.

TABLE 5

An analysis of female sterility in Holsteins. Results of mating 100B to his own daughters.

	FERTILE	STERILE	
Observed	40	4	
Calculated[a]	38.5	5.5	
			$\chi^2=0.467$

[a] Calculated on the basis that 100B and half of his daughters are heterozygous.

Table 5 summarizes the results of mating 100B to his own daughters. The numbers involved are satisfactory and all the results indicate that 100B is heterozygous for a gene for female sterility.

DISCUSSION

After presenting the available data, some of which are fragmentary, several points merit further discussion. The first concerns the validity of the conclusion that the sterility encountered is sex-limited and affects females only. The authors, though mindful of the differential origin and function of the male and female genital tracts, base the conclusion on the following considerations: (1) All the sterility actually encountered was limited to females. A substantial number of the sons of bulls that produced sterile daughters were used as sires,

and all proved to be fertile. (2) Sire 300D bred as a homozygous individual for female sterility, and if the sterility had not been sex-limited he should have been sterile.

The second question concerns the number of female sterile genes involved. In the discussion of the Jerseys, in a preceding section, it was not clear whether the genes for female sterility carried by 300 and 300D were identical or different. The Jerseys and Holsteins were never crossed, and observation must be the only basis for considering the relation of the female sterility found in the two breeds. The most striking difference between the sterile Jerseys and Holsteins is in the heat periods. Whereas all the Jerseys came in heat, three of the five sterile Holsteins were never observed to do so. There are no absolute data available for determining the genetic relation of the female sterile gene found in the Holsteins and the one (or ones) found in the Jerseys. It is possible that different genes are involved.

This study indicates that genes for female sterility are of common occurrence. Although, admittedly, some sterility encountered could have been of a non-hereditary type, it is significant that all the sterility actually noted in the herd can be accounted for by one or more specific genes. No attempt was made to study the specific etiology of the female sterility. Perhaps other investigators who have accumulated data of a similar nature over a period of years may publish their results. For this reason, the identity of each sire that produced sterile daughters is given below:

Herd Number	Registered Name	Registry Number
300	Octavia's Rinda Lad	188257
300C	Gravity's Exile of Lusscroft	162551
300D	Pogis Torono Experimenter	177266
333C	California Rinda's Choice	259802
370A	California Napoleon Nick	316846
100B	Bear Valley Ormsby Esther	518683

The incidence of sterility among heifers in cattle populations has a distinct bearing on the problem of hereditary sterility. ALBRECHTSEN (1917) made an extensive study of sterility in Danish cattle. He found that the range of sterility among heifers of the individual herds observed varied from none to 9 percent with a mean of 4.8 percent for 22 herds involving 2209 heifers. ECKLES' (1929) analysis of 29 years of breeding records from the University of Minnesota and Branch Stations reveal 7.4 percent sterility among 311 heifers two years of age. There was no attempt at genetic analysis of sterility in either of these studies. The percentage of sterility observed in heifers of the California herd (table 2) is of about the same magnitude as that observed by ALBRECHTSEN and ECKLES.

ERIKSSON (1944) found 25 percent of sterility in a selected population of Swedish Highland cattle. This sterility was accompanied by a hypoplasia of the genital tract that affected both bulls and heifers. One autosomal recessive

gene with incomplete penetrance accounted for the sterility. Since the sterility found in the California herd is limited to females, obviously it is genetically different from the condition studied by Eriksson.

FINCHER and WILLIAMS (1926) report sterility from a Holstein herd that parallels the California observations in being sex limited. A bull bred to unrelated cows produced large, vigorous, normal progeny. The bull calves were sold for breeding; and according to the evidence all were fertile. The heifers were retained in the herd and bred back to their sire. All proved fertile; 23 female calves and several male calves resulted from the sire-daughter mating. In general the fertility of the inbred males appears to have been satisfactory. Many of the 23 inbred heifers however, proved to be sterile, although autopsies revealed that their ovaries and vulvae were normal throughout. Parts of the genital tract derived from the Mullerian ducts were suppressed and abnormal. The greatest anomalies occurred in the cornu, cervix and vagina, whereas the fallopian tubes were apparently normal.

FINCHER and WILLIAMS suggest that heredity and incestuous matings may be responsible for this aberration, but they offer no clear-cut genetic explanation. From their data it is possible to offer a completely satisfactory genetic hypothesis. They classified 23 daughters produced by sire-daughter matings as follows: 13 sterile or "technically" sterile, three "technically" fertile, and seven fertile. This gives a ratio of 13 sterile to 10 fertile. If the sire is homozygous for the gene for female sterility and if the maternal granddams of the 23 inbred heifers are homozygous normal, half the inbred daughters should be fertile and half sterile. This apparently is a clear-cut case of a single recessive autosomal gene conditioning female sterility, the Holstein sire being like the California Jersey sire 300D, homozygous for female sterility. It would be interesting to know whether any cases of female sterility studied in the California herd are genetically identical with the type reported by FINCHER and WILLIAMS. This study also offers a completely satisfactory explanation for the female sterility so well established in the famous Bates' Duchess family of Shorthorns.

Even though each occurrence of absolute female sterility in the California herd can be accounted for by a specific gene, there still remains the problem of quantitative female fertility in the herd. Some of the cows produce only one calf, or a few, whereas others have extended records of reproductive longevity. The quantitative phase of fertility is probably more subject to environmental factors and is therefore more difficult to analyze. Such a study of the herd should be attempted, however, when time permits.

SUMMARY

A qualitative analysis of female fertility and sterility was made for all Jerseys and Holsteins of the CALIFORNIA EXPERIMENT STATION herd that have reached the age of reproduction during the past 25 years. The Jerseys involve 266 cows sired by 16 bulls; the Holsteins, 94 cows sired by two bulls. The terms fertility and sterility as used in this report are defined. All the sterility observed

was limited to females. No quantitative study of female fertility was attempted.

Only a few of the bulls produced sufficient progeny for an adequate genetic analysis. The use of sire-daughter matings permitted a Mendelian analysis for genes conditioning female sterility.

Five Jersey bulls and one Holstein produced a total of 20 sterile daughters from outcrossed and inbred matings. Three of the original, unrelated Jersey sires had sterile daughters. The available data, however, permitted an analysis of only two; one of the original sires was analyzed directly, and the other indirectly by means of a son and a grandson. The Holstein bull that produced sterile heifers was used extensively in sire-daughter matings. The female sterility transmitted by each of the bulls tested followed a single autosomal recessive factor with a sex-limited pattern of inheritance.

It was not determined whether the original bulls carried the same or different genes for female sterility. Judging from the evidence, the original population of Jersey and Holstein cows carried a gene for female sterility, the frequency value being approximately .1 or less.

All the sterile females observed could be accounted for by a specific gene for sterility. Judging from this and other studies, heredity plays a more important role in female sterility than is generally suspected.

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LOCATION OF THE CENTROMERES ON THE LINKAGE MAPS OF MAIZE[1]

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IN RELATING genetic data to the morphology of the chromosomes in maize, the relation of gene loci to the position of the centromere, or region of spindle attachment, is of primary interest and importance. The relation of the genes to each other on the linkage maps is established directly from crossing over percentages, but the physical position of the genes in the chromosomes must necessarily be determined indirectly from both genetical and cytological data, since suitable techniques for the visual identification of individual genes are not yet available.

Chromosomal alterations that produce both genetical and visible cytological effects may be used to locate the position of the genes in the chromosomes. Of these, the most useful are the translocations, inversions and deletions that produce both phenotypic effects suitable for mapping with the techniques used for genes and visible disturbances of the normal synaptic relations by means of which their location in the chromosome can be determined. This correlation of loci on the genetic maps with specific regions of the chromosomes concurrently establishes the location of the genes with reference to the centromere and other differentiated regions of the chromosome.

The locations of the centromeres on the linkage maps were determined chiefly from translocations which were observed cytologically at the midprophase of the first meiotic mitosis. The cytological determinations were subject to minor errors of interpretation due to failure of pairing and non-homologous association of the chromosomes in the region of exchange of segments. A single case of duplication, that of a telocentric half-chromosome (RHOADES 1936, 1940) located the centromere of chromosome 5 with a high degree of precision. Deficiencies have been useful in correlating the genetic maps with the distal regions of the chromosomes, less so for the regions near the centromeres. However, the internal deficiencies and ring fragments studied by MCCLINTOCK (1938, 1941) delimited within narrow boundaries certain locations near the centromere of chromosome 5.

Translocations may be identified by the sterility they produce when in the heterozygous condition. Thus their position in the linkage maps can be established in much the same manner as are the positions of dominant genes. The

[1] Cooperative investigation of the Division of Biology, CALIFORNIA INSTITUTE OF TECHNOLOGY, Pasadena, California, the Department of Botany, NEW YORK STATE COLLEGE OF AGRICULTURE, CORNELL UNIVERSITY, Ithaca, New York, and the Division of Cereal Crops and Diseases, Bureau of Plant Industry, Soils, and Agricultural Engineering, Agricultural Research Administration, U. S. DEPARTMENT OF AGRICULTURE.

sequence of translocations within a given region between two genes cannot be determined satisfactorily, and measurement of map distances are unreliable due to various amounts of suppression of crossing over. But the order of the genes and translocations on the linkage maps can be determined reliably and can be checked in the homozygous translocation.

Homozygous translocations are of especial value in mapping the centromeres. If it can be determined on which side of the centromere the translocation has occurred in the one chromosome, a simple test for linkage with known genes may tell which arm of the other chromosome is involved. As in the case of T2-3b, the map location of the translocation in chromosome 2 is to the right of *v4* well out on the long arm. It is near *ts4* in chromosome 3. In the homozygous translocation the linkage of *B* and *v4*, which are on opposite sides of the centromere in chromosome 2, with *ts4* places the break in chromosome 3 between *ts4* and the centromere; and the undisturbed linkage of *ts4* with *lg2*, which is approximately 30 units to the right of *ts4* places the break in the long arm of chromosome 3. In this manner much information relative to the location of genes and centromeres often can be obtained even in the absence of cytological observations. Moreover, cytological observations also may be checked in the same manner.

An effort has been made to present only such information as is needed to locate the centromeres within narrowest boundaries. The data were selected to show for each chromosome the nature of the evidence on which our conclusions are based, and to show the limits of our actual information.

Chromosome 1

Information on translocations in the short arm of chromosome 1 was summarized by ANDERSON in 1941. The gene *P* is about two-thirds of the distance out on the short arm. A minimum map distance from *P* to the centromere may be determined from T1-9a which is known to be located in the short arm. On the basis of 730 plants, the percentage of crossing over between *P* and T1-9a was found to be 21.2 ± 2.5. Thus the location of the centromere on the linkage map is 21.2 units or more to the right of *P*.

A number of translocations in the long arm of chromosome 1 give less than 5 percent of crossing over with brachytic. These are distributed from about L.2 to about L.6. The gene *br* is probably located in the neighborhood of L.3 or L.4. Only two of the translocations in the long arm are definitely placed to the left of *br*. T1-6a was reported by COOPER and BRINK (1931) and BRINK and COOPER (1932) to be in the long arm of chromosome 1 a short distance from the centromere. From their diagrams and figures a position of about L.2 is indicated, which is also in accord with other data. The map position, based on 75 plants, is given as 13.4 units to the left of *br*. T1-6b has been described by BURNHAM (1932). The locus in chromosome 1 is given as L.25. Very good linkage data involving 952 plants place the translocation to the left of *br* with 3.8 percent of crossing over. (Data by BURNHAM cited by EMERSON, BEADLE and FRASER 1935.)

These data show merely that *br* is between one-quarter and one-half the distance out on the long arm. The map position of the centromere must be somewhere between the locus of T1-9a, 21.2 units to the right of *P* and the locus of T1-6a, 13 units to the left of *br*. This is a very long region. If crossing over were equally distributed over this portion of the chromosome, we might expect the location of the centromere to be about midway between *P* and *br*.

Chromosome 2

The map location of the centromere can be rather closely delimited by a number of translocations in the interval between *ts* and *v4*. Several of these will be considered. T2-9b is located cytologically at 2S.1 and 9L.2. Linkage tests give the order definitely as *B-ts-T-v4*. Crossing over between the nearest genes was:

ts-T = 33/662 = 5.0
T-*v4* = 121/1542 = 7.8

Since the break in chromosome 9 is known to be in the long arm (ANDERSON 1938), the *wx* gene must be carried in the 9^2 chromosome. Tests of linkage relations in the homozygous translocations were used to verify the location of the break in chromosome 2. These tests gave the following results, showing that the break is between *ts* and *v4*.

B-*ts* = 86/319 = 26.3
ts-*v4* = 108/195 = 55.4, or independence
wx-*B* = 159/721 = 22.1
wx-v4 = 2571/5056 = 50.9

The linkage of *wx* with *B* and its independence of *v4* establishes the break in the short arm of chromosome 2 between *B* and the centromere. The linkage of *B* and *ts* shows that the break is to the right of *ts*, and the independence of *ts* and *v4* locates the break between those genes. Thus the centromere in chromosome 2 is at least five units to the right of *ts*.

T2-5a was studied by RHOADES (1933) and described cytologically as in the long arm of chromosome 2 near the centromere. Linkage tests give the order as *B*-T-*v4* with 7.3 percent of crossing over between T and *v4*.

T2-10a is located at L.2, with the break in chromosome 10 well out on the long arm, two or three cross-over units to the left of *g*. The order on chromosome 2 is *ts*-T-*v4*, and the data on crossing over are as follows:

ts-T = 52/384 = 13.5
T-*v4* = 74/1145 = 6.5

Linkage data in the homozygous translocation are as follows:

B-ts = 50/282 = 17.7
B-g = 42/205 = 20.6

Since *g* is distal to the break in chromosome 10, the *B-ts* section of chromosome 2 must include the centromere—that is, the translocation must be in the long arm of chromosome 2.

These data may be summarized as follows:

T2-9b	*ts*-5.0-T-7.8-*v4*	Short arm
T2-5a	*ts*-T-7.3-*v4*	Long arm
T2-10a	*ts*-13.5-T-6.5-*v4*	Long arm

The centromere must be five or more crossover units to the right of *ts* and 7.3 or more units to the left of *v4*. Since there is usually some suppression of crossing over in the heterozygous translocation, the total map distance of the *ts*-*v4* interval is uncertain. The normal value is probably about 20 units. The centromere is probably a little closer to *ts* than to *v4*.

Chromosome 3

The summary of translocations involving chromosome 3 published by ANDERSON and BRINK (1940) places the centromere in the general neighborhood of *ts4*. Since then, additional data on T2-3b has indicated that *ts4* is in the long arm of chromosome 3. This translocation shows about 4 percent of crossing over with *v4*. The order is probably *B*-*sk*-*v4*-T. Linkage tests in homozygous T2-3b stocks give the following crossover values:

B-*sk*	=38/399=9.5
B-*v4*	=128/289=44.3
B-*ts4*	=496/1171=42.4
ts4-*lg2*	=27/135=20.0
v4-*ts4*	=10/59=17.0

These data all agree in placing the translocation beyond *v4*, consequently in the long arm of chromosome 2. The linkage of *ts4* with *B* and *v4* in the homozygous translocation places the break in chromosome 3 between the centromere and *ts4* and shows that it is the long arm that is involved. From this it may be concluded that the centromere is to the left of *ts4*—that is, between *d1* and *ts4*.

Chromosome 4

A number of translocations in the proximal regions of both arms of chromosome 4 adjacent to the centromere all show close linkage with *su*, usually accompanied by much suppression of crossing over. These data indicate that the centromere is in the general region of the *su* locus.

Translocation 4-5*d* has been placed by linkage in chromosome 4 between *su* and *Tu;* in chromosome 5 between *bm* and *pr*. The frequency of crossing over between the translocation and *su* was 14/493 or 2.8 percent; between *bm* and the translocation it was 11/439 or 2.5 percent. In the homozygous translocation, the genes *Ts5* and *su* were linked, and these genes were also linked to both *bm* and *a2* from chromosome 5. RHOADES (1936) has shown that the centromere of chromosome 5 is in the very short region between *bt* and *bm*, a short region of about 1 unit. This is much less than the observed crossover value of 2.5 between *bm* and the translocation. Therefore, the location of the translocation must be in the long arm of chromosome 5, with *bm* remaining

with the centromere. The linkage of *Ts5* and *su* with *bm* in the homozygous translocation must involve a break in the short arm of chromosome 4 between *su* and the centromere. Thus the map position of the centromere of chromosome 4 must be at least 2.8 units to the right of *su*—that is, between *su* and *Tu*.

Translocation 2-4c is very near the centromere in the short arm of chromosome 4, and far out on the long arm of chromosome 2. The linkage relations are as follows:

su-9.1-T-30.8-*Tu*
v4-19.9-T-29.3-*Ch*

Linkage tests with the homozygous translocation confirm the order in chromosome 4 and give the further data:

su-v4 =401/1057=37.9
su-Ch =247/525=47.0 (independence)
Tu-Ch=193/429=44.9

The linkage of *su* with *v4* places the translocation between *su* and the centromere and indicates a position for the centromere 9 units or more to the right of *su*. This confirms the conclusion drawn from translocation 4-5d.

Chromosome 5

The position of the centromere in relation to the known genes of chromosome 5 was determined accurately by RHOADES in 1936, with the aid of a fragment of chromosome 5, which apparently consisted of the centromere and the entire short arm of the chromosome. In the metaphase of the first meiotic division in the microsporocytes the fragment formed a trivalent with the two normal number 5 chromosomes in approximately half of the cells; in the remainder of the cells it was present as a univalent that was rarely included in either daughter nucleus. From the known cytological behavior of the fragment the expected backcross ratio from fragment plants of the constitution *AAa* with *a* in one of the normal chromosomes was calculated to be 5A:3a or 37.5 percent of recessives. This ratio differs sufficiently from the ordinary 1:1 backcross ratio of disomic inheritance so that, with the aid of the fragment chromosome, genes located in the short arm could be distinguished from those located in the long arm of chromosome 5.

Another test employed by RHOADES to identify the genes in the short arm was the occurrence of fragment-carrying plants homozygous for the recessive gene in the backcross progenies of fragment plants carrying a recessive allele in one of the normal number 5 chromosomes. If the locus under consideration was in the short arm, none of the fragment-carrying plants would be homozygous for the recessive allele, barring rare exceptions resulting from chromatid crossing over.

Utilizing these tests, it was found that the *a2* and *bm* loci were in the short arm and *bt*, *pr*, *ys*, *v2*, and *v12* were in the long arm of chromosome 5.

MCCLINTOCK (1938, 1941) studied deficiencies in the region about *bm* and

also placed *bm* in the short arm close to the centromere. The available data on translocations are in agreement with the findings of RHOADES and MCCLINTOCK.

The centromere is located in the very short region between *bm* and *bt*.

Chromosome 6

Translocation 6-9b, about one-fourth of the way out on the long arm, is to the right of *Y* but very closely linked to it. Five other translocations are recorded cytologically at about L.2 or L.25. These are T 1-6c, 2-6c, 4-6a, 4-6b, and 4-6c. All are closely linked with *Y* and definitely to the left of *Pl*. When heterozygous, all show a reduction of crossing over between *Y* and *Pl* to 5 percent or less. Proven crossovers with *Y* have not yet been obtained for study. With so much suppression of crossing over, little can be inferred as to the location of the *Y* locus with reference to the centromere. Translocations in the satellite or nucleolar region have given less than 20 percent of crossing over with *Y*. Data on translocations between the centromere and the nucleolar region are too meager to give any satisfactory evidence as to the position of the centromere.

The map location of the centromere may be very near *Y*, or to the left of *Y*, probably not more than five or ten units.

Chromosome 7

Two translocations, T1-7b and T2-7b, place the genes *ra*, *gl*, and *ij* on the long arm. Translocation 1-7b is far out on the long arm of chromosome 1 and about one-fifth of the way out on the long arm of chromosome 7. The map position of the break in chromosome 1 is a little to the right of *br;* in chromosome 7 it is a trifle less than one unit to the left of *ra*. This is confirmed by data on the homozygous translocation showing *ra* linked to *P* and *br* and independent of *bm2*. The translocation is therefore to the left of *ra* and between it and the centromere.

Translocation 2-7b is about one-fourth of the distance out on the long arm of chromosome 7 and is in about the same relative position on the long arm of chromosome 2. Linkage tests place it near *ra*, with slightly over one percent of crossing over. Linkage tests in the homozygous translocation show linkage of *ra* and *gl*, which indicates that the translocation is to the left of *ra*. This is also confirmed by the linkage of *B* and *ra* (*B-ra* = 167/462 = 36.1). Since *B* is in the short arm of chromosome 2 and thus in the 2^7 chromosome, *ra* must be in the translocated portion of the long arm of chromosome 7.

Three translocations in the short arm of chromosome 7 also have been tested for linkage with *ra*. These together with the two described above have given the following data:

T1-7d	S.4	5/231 = 2.2
T2-7c	S.1+	24/376 = 6.4
T5-7	S.1	14/153 = 9.2
T1-7b	L.2	5/546 = 0.9
T2-7b	L.2+	4/364 = 1.1

The centromere is to the left of *ra*, probably only a few units. Its relation to *v5* is unknown.

Chromosome 8

The only genes known to be located in chromosome 8 are in the distal region of the long arm. From the data of ANDERSON (1939), the location of the centromere must be 30 units or more to the left of *ms8*.

Chromosome 9

Information on chromosome 9 has been summarized by ANDERSON (1938). Translocation 5-9a is located in the short arm near the centromere and is to the right of *wx* with about 2 percent of crossing over (BURNHAM 1934a). This places the centromere at least two units to the right of *wx*. Translocation 3-9a, in the long arm gave only 3.6 percent of crossing over with *wx*, indicating that the centromere is probably not far beyond the minimum of two units. The gene *v* has not been located definitely but is believed to be in the long arm not far from the centromere (BEADLE 1932; BURNHAM 1934b). Its map position is 12 units from *wx*.

Chromosome 10

The only chromosome 10 genes which have been adequately used in tests with translocations are *g* and *R*. Both are located in the distal part of the long arm. Translocations to the left of L.3 have given from 9 to 23 percent of crossing over with *g*. Probably different amounts of suppression are involved.

Crossing over T-*g*

8-10a	S.6	104/613=17.0
8-10c	S.4	122/535=22.8
9-10b	L.1−	12/135= 8.8
6-10a	L.1	33/342= 9.6
3-10a	L.1+	74/471=15.7
1-10a	L.3	21/137=15.3

The centromere must be placed at least 15 units to the left of *g*. Its relation to such genes as *nl*, *li*, and *sp2*, previously mapped to the left of *g* by EMERSON et al. (1935) or by RHOADES and RHOADES (1939), cannot be determined from present data. The gene *Rp*, mapped at 43 units to the left of *g* by RHOADES and RHOADES (1939), is placed in the distal one-fourth of the short arm by the earlier studies of V. H. RHOADES (1935).

LINKAGE MAPS

For graphic representation, linkage maps of the ten chromosomes showing the location of the centromeres are presented in figure 1. Only the better known genes, or the genes used in the present studies are listed. Genes whose order in relation to the centromere is unknown or in much doubt are omitted. Untested genes near the centromere whose location is uncertain are enclosed in parentheses.

These maps bring up to date and replace similar maps published earlier by RANDOLPH (1941).

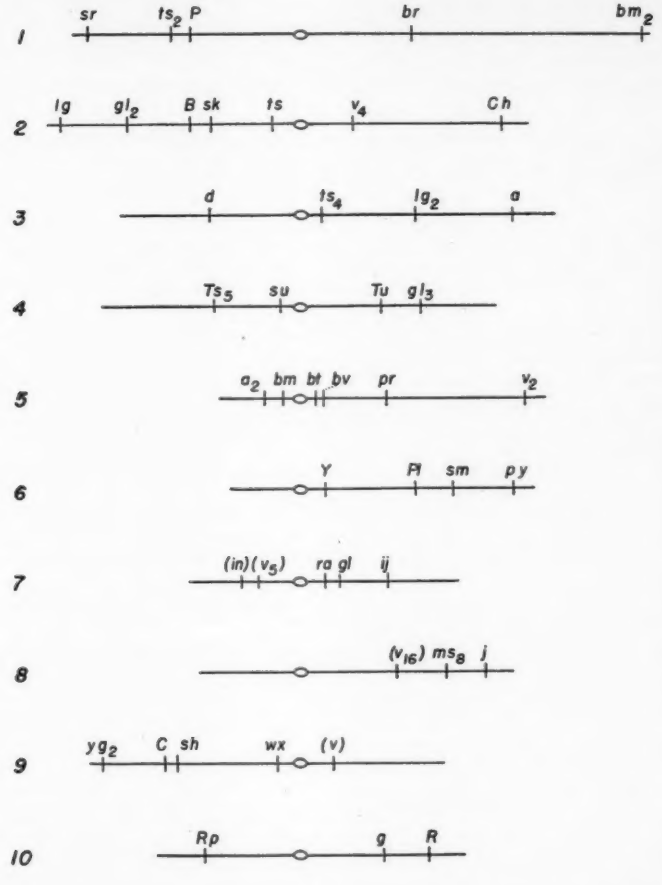

FIGURE 1.—Approximate locations of the contromeres on the linkage maps of selected genes in maize.

SUMMARY

The evidence relating to the locations of the centromeres on the linkage maps of maize has been presented, and, so far as can be determined from the available data, these locations are as follows:

Chromosome 1. Midway between *P* and *br*.

Chromosome 2. Between *ts* and *v4* but closer to *ts*.

Chromosome 3. A short distance to the left of *ts4*.

Chromosome 4. A few units to the right of *su*.

Chromosome 5. Between *bm* and *bt*.

Chromosome 6. Near, or to the left of *Y*.

Chromosome 7. A few units to the left of *ra*.

Chromosome 8. Thirty or more units to the left of *ms8* and *j*. No genes known in the region.

Chromosome 9. A few units to the right of *wx*, probably between *wx* and *v*.

Chromosome 10. Fifteen or more units to the left of *g*.

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HETEROSIS RESULTING FROM DEGENERATIVE CHANGES

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HERITABLE variations in inbred strains of maize occur infrequently. All the mutations so far found either do not increase the amount of growth and productiveness or clearly reduce the plants in some degree (JONES 1924, 1939, 1944; SINGLETON 1943). Several changes have been noted recently and reported in a preliminary way (JONES 1944) which reduce the vigor of the inbred plants but which increase the growth of their hybrid offspring when they are crossed back to the normal line from which they were derived and from which they differ by what appears to be a single allele. These mutations and their effects in hybrid combinations are described in detail here.

NARROW LEAF

The narrow leaf variation originated in an inbred line of Lancaster Surecrop designated as CI 4-8, produced by the UNITED STATES DEPARTMENT OF AGRICULTURE. When this line was received, it had been self-fertilized for more than ten generations. The narrow leaf condition was first noticed in a uniform progeny in which all the leaves were distinctly narrower than the normal line

TABLE 1

A comparison of the narrow leaf variation with the normal line (CI 4-8), from which it originated; and the first generation hybrid between the normal and mutant lines.

DESIGNATION OF LINE	WEIGHT OF EARS PER PLOT	HEIGHT OF STALK	LEAF WIDTH	STALK DIAMETER	DATE OF TASSELING	DATE OF SILKING
Normal C	282	65.0	88.9	20.8	15	20
Normal I	314	72.0	91.0	20.4	15	17
Normal C×normal I	296	67.0	92.3	20.4	14	19
Narrow leaf	432	75.5	65.8	17.4	11	12
F_1 normal C×narrow	873	79.4	82.5	19.5	11	14
F_1 normal I×narrow	925	79.3	81.9	19.3	11	14
F_1 narrow×normal C	846	78.0	82.0	19.3	11	14
Mean, three normal parents	297	68.0	90.7	20.5	15	19
Mean, normal and narrow parents	365	71.8	78.3	19.0	13	16
Mean, three F_1	881	78.9	82.1	19.4	11	14
F_1 mean−parental mean	516	7.1	3.8	.4	−2	−2
F_1 mean−larger or earlier parent	449	3.4	−8.6	−1.1	0	2
Significant difference	242	2.8*	5.0	1.2	2	3
Percentage increase over larger parent	104	5				
Percentage increase over parental mean			5	2		

* On .05 level, all other significant differences on .01 level.

from which it deviated. The normal 4-8 line grown in Connecticut (designated C in table 1) was compared with the same line obtained recently from the ILLINOIS AGRICULTURAL EXPERIMENT STATION (designated I). Both lines are similar in yield of grain, width of leaf, diameter of stalk, and date of tasseling. They differ significantly in height of plant and date of silking, showing that some heritable variation may have occurred during the many years they have been separated.

These two normal lines were inter-crossed and the first generation hybrid compared. The inter-crossed normal plants do not differ significantly from the self-fertilized normal plants, showing that no variations affecting heterosis to a discernible degree had occurred in the two sub lines. The differences between the two normal lines are small when compared to the deviation that the narrow leaf line shows. This line is significantly taller, narrower in leaf width and stalk diameter, and earlier in flowering, as shown in table 1. It is not significantly more productive of grain. In previous years the narrow leaf line was notably less productive, but in the very dry season of 1944 the earlier maturity and reduced leaf area gave this line a slight advantage.

The results of three first generation crosses between the normal and narrow leaf lines are given in table 1. All are alike within the limits of the probable error and the average of the three crosses exceeds the more productive parent by 104 percent in yield of grain and 5 percent in height of stalk. In leaf width and stalk diameter and time of flowering the crosses are intermediate between the two parents but do not exceed the parental mean by a significant amount.

The surprisingly large amount of heterosis resulting from such a small hereditary difference was indicated in a preliminary test the previous year (JONES 1944), and is fully confirmed by this more complete test. All entries were replicated four times in a randomized block arrangement. Nearly complete stands were obtained by planting an excess of seed and thinning after the seedlings were well started. Each entry consisted of one row 15 feet long. Weight of ears is in grams per plot, height of plants is in inches, leaf and stalk width in millimeters. Date of tasseling and silking is the number of days from the first of August. By adding 65 days the number of days from planting to flowering may be obtained. Significant differences are calculated by the usual procedure and are given on the .01 level except as otherwise noted.

DWARF PLANTS

Plants about half the normal height originated in an inbred line known as Illinois Hy. This is a standard corn belt inbred used in many commercial hybrids. The dwarf plants were first noted in an increase field grown by a seedsman in Illinois. Self-fertilized plants produced only shortened plants in subsequent generations. Dwarf plants (fig. 1) differ from normal plants largely in a shortening of the internodes. Leaves are somewhat reduced in length and appear to be stiffer and held more erect. Both types of plants have about the same number of leaves. Tassels and ears of the dwarf plants are smaller and kernel size is also reduced. Total production of grain is noticeably less. Dwarf

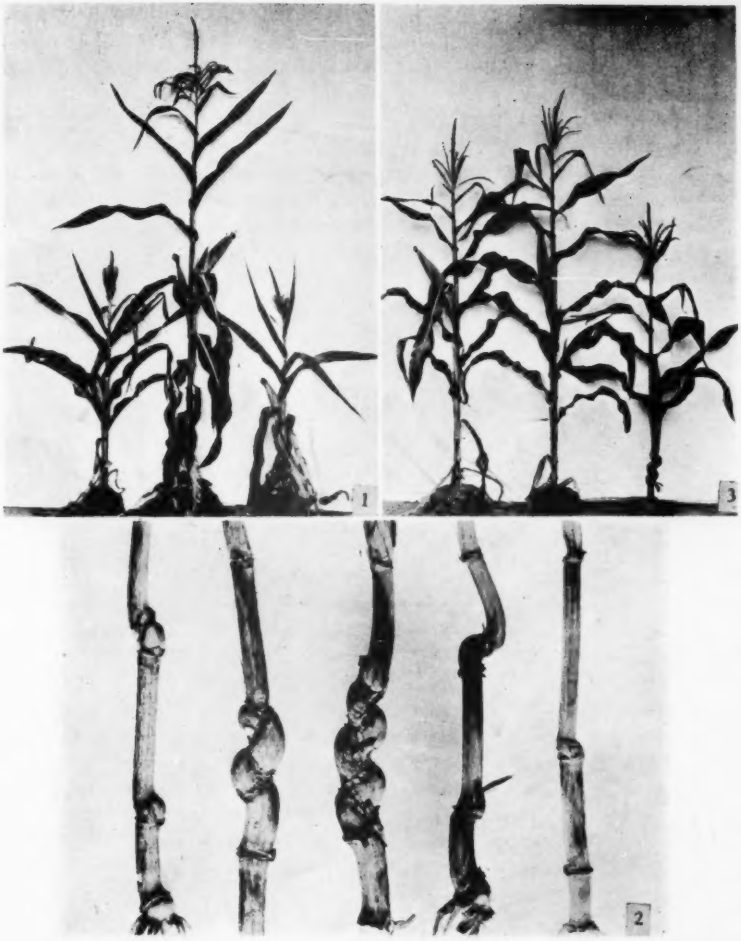

FIGURE 1.—Normal and dwarf plants from the Hy inbred.
FIGURE 2.—Variable expression of the crooked stalk character.
FIGURE 3.—Crooked stalk and pale top on the right produced by mutation from the normal Kr inbred on the left. First generation hybrid plant in the center.

plants flower about the same time as normal. This variation is similar to the reduced plant described by SINGLETON (1943).

The dwarf plants, being so much smaller, were not included in the replicated yield test for the reason that they would introduce a competitive effect. No accurate measure of yield and date of tasseling and silking were obtained for the dwarf variants. In appearance this variation resembles brachytic, but has not been tested with this gene. The first generation cross of dwarf and normal backcrossed to the recessive dwarf, in a preliminary test, produced 16 tall and

TABLE 2

A comparison of the dwarf plant variation with the normal line (Illinois Hy) from which it originated and the first generation hybrid between the normal and mutant lines.

DESIGNATION OF LINE	WEIGHT OF EARS PER PLOT	HEIGHT OF STALK	DATE OF TASSELING	DATE OF SILKING
Normal A	624	74.2	10	14
Normal B	692	76.8	10	15
Dwarf plant		43.3		
Dwarf×normal A1	1224	76.3	8	12
" " A2	1480	82.3	8	11
" " B1	1142	73.4	9	13
" " B2	1348	78.4	9	13
Mean, two normal parents	658	75.5	10	15
Mean, normal and dwarf parents		59.4		
Mean, four F1	1299	77.6	9	12
Difference, F1 mean—parental mean		18.2		
Difference, F1 mean—larger parent	641	2.1	−1	−3
Significant difference	332	4.1		
Percentage increase over larger parent	98	3		

11 short plants. A frequency distribution for height of plant in a self-fertilized second generation progeny is as follows:

Height classes in inches	15–24	25–34	35–44	45–54	55–64	65–74	75–84
Number of individuals	1	4	10	9	7	11	2

The dwarf mean height of 43.3 and the normal mean height of 75.5 fall either within or close to the same class limits as the two modes in the F2 frequency distribution. This preliminary evidence indicates that this deviation is a recessive character due to a single mendelizing difference.

In table 2 are given the results of crossing the dwarf plant with the normal line from which it originated. Two normal Hy lines, that had been separated for several generations, are compared. Differences between these normal lines are small and well within the limits of experimental error. These two normal lines were not inter-crossed, but both were crossed in subsequent generations with the dwarf variation. The differences between the first generation crosses and the higher yielding normal parent are nearly twice the significant difference in weight of ears, thus showing a large amount of heterosis. There is no sig-

nificant difference in height between the first generation crosses and the normal tall parent, but considering the great disparity in the stature of the parents the excess of the hybrid over the parental mean is notable. The crossed plants made this double yield in a shorter time as indicated by the one day less time to tasseling and three days less time to silking. The heterotic plants are visibly greener, more robust, and produced seeds having a brighter color and larger kernels.

PALE CHLOROPHYLL AND CROOKED STALKS

An inbred strain of corn originally out of Krug Yellow Dent, released by the UNITED STATES DEPARTMENT OF AGRICULTURE as CI Kr 187-2, has been outstanding for its dark green chlorophyll color and strong sturdy stalks. When received it had been inbred for many generations. After being propagated by sib-pollination for several generations in Connecticut, five progenies from single self-fertilized plants were grown in 1942. In four of these progenies several plants were noted during the gr wing season as smaller and later in flowering. These plants were marked and self-fertilized about a week after all the other plants were past the pollinating stage. At the end of the season these later plants were about as tall and productive as the other plants in the same progenies and did not differ from them in any respect.

Progenies from these plants grown the following year were examined closely throughout the season. Before flowering they were somewhat lighter in color, especially at the base of the whorl of leaves at the top of the plant, and this condition is designated pale top. It was noted that several progenies were segregating for this character, and one appeared to be homozygous pale top. It was also noted that some of these progenies were segregating for the crooked stalk condition shown in figure 2. One plant of this type had been noted and self-fertilized the previous year. Some of the internodes below the ear were shortened and bent so that the nodes were placed at an angle. The number and arrangement of these abnormal internodes varied considerably within each progeny, as shown in figure 2. The number of internodes affected ranged from one to five. In most cases the abnormal nodes were all together, in other cases normal internodes alternated between abnormal ones. One progeny was homozygous for both pale top and crooked stalks. Two progenies were all pale top and segregating for crooked stalks. Others were all crooked and segregating for pale top. Some progenies have remained free from both deviations. Table 3 shows the number of deviating plants of each type in the segregating progenies during three successive generations.

Only one plant with a crooked stalk was noted in 1942, as stated above. In the next generation the self-fertilized offspring of this plant were all crooked. Two other progenies from sib plants in this number 2 line were also segregating. One progeny from the number 1 line, in which no crooked stalks were noted the first year, also segregated, and two progenies in the number 3 line had all plants crooked. It is possible that the crooked stalk condition was overlooked in some of these parental plants, since all plants were not carefully examined

TABLE 3

Segregation of pale leaf and crooked stalk in three generations of self-fertilized progenies of CI Kr 187-2.

PROGENY NUMBER	CHLOROPHYLL		STALK	
	GREEN	PALE	STRAIGHT	CROOKED
1	13	3	All	
2	12	3	14	1
3	13	3	All	
4	All		All	
5	15	1	All	
	—	—		
Total 1942 segregations	53	10		
1–1	All		All	
1–2		All	15	1
2–2	9	8		All
2–3		All	15	1
2–4		All	11	7
3–5	10	6		All
3–6		All		All
4–1,2,3,4,5	All		All	
	—	—	—	—
Total 1943 sergegations	19	14	41	9
1–2–1		All	8	1
2		All	All	
3		All	All	
4		All	14	3
5		All	All	
2–4–1		All	4	4
3–5–1	4	2		All
2	12	3		All
3	All			All
3–6–1		All		All
2		All		All
3		All		All
	—	—	—	—
Total 1944 segregations	16	5	26	8
Total all segregations	88	29	81	18
Expected 3:1	88	29	75	25

by removing the leaf sheaths from all nodes below the ear. It is also possible that some lines were segregating without showing any recessive individuals, these either failing to germinate or being thinned out. There is also variability in the expression of this character.

All lines that are all pale or all crooked or both have remained so in the two succeeding generations, and several progenies of each type have been grown. Lines homozygous for only pale top and only crooked stalk have been separated. All of this evidence indicates quite clearly two recessive genes that

are either independent or not closely linked. Further information to clarify this point is being obtained.

During the past season three other variations have appeared in this Kr line which also seem to be recessive deviations of a degenerate nature. These are flat cob, streaked chlorophyll, and narrow leaves. Segregation is not as clear cut as with the first two characters described, and homozygous progenies have not as yet been obtained. Variations of this type were not noted before the 1944 season in this family. Apparently a condition of high mutability has arisen in this continuously inbred family. The possibility of outcrossing is ruled out, since the resulting hybrid vigor would be immediately apparent.

The same lot of seed of a progeny that had given all plants crooked and pale during the summer was planted again during the winter in the greenhouse and

TABLE 4

A comparison of the pale leaf and crooked stalk variation with the normal line (CI Kr 187-2) from which it originated and the first generation hybrid between the normal and mutant lines.

DESIGNATION OF LINE	WEIGHT OF EARS PER PLOT	HEIGHT OF STALK	DATE OF TASSELING	DATE OF SILKING
Normal	1083	66.6	11	15
Pale and crooked	472	52.7	20	22
Normal×pale and crooked	1311	71.1	14	17
Pale and crooked×normal	1326	74.0	14	17
Mean, two F_1	1319	72.6	14	17
Mean, normal and pale, crooked parents	778	59.7	16	19
F_1 mean—parental mean	541	12.9	−2	−2
F_1 mean—larger or earlier parent	236	6.0	3	2
Significant difference	226*	4.1		
Percentage increase over larger parent	22	9		

* On .05 level, all other significant differences on .01 level.

produced typical pale top individuals but no crooked stalks. The following winter seed of the same lot was again grown. The plants were divided into two lots, one of which received extra illumination for several hours each day, extending the period of light to correspond more nearly to the normal summer growing season. The other lot received no additional light. Both lots had one plant with a crooked stalk; the remaining plants were all normal. Apparently the period of daylight has little to do with the expression of this character. The lower temperature or other conditions associated with greenhouse culture must be responsible for the failure of the abnormal stalk condition to appear in all plants as it does during the summer under field conditions.

The homozygous pale and crooked plants were crossed reciprocally with the normal line which has shown no deviating plants in any progenies during three generations of close observation. Representative plants of the normal and deviating parents with the first generation hybrid are shown in figure 3 with the bottom leaves removed to show the condition of the stalks. The pale

chlorophyll is not apparent at this stage of development, but the reduced size of plant and ear is quite noticeable. All of the first generation crossed plants were normal, showing complete dominance over pale top and crooked stalks. Table 4 gives the average weight of ears, height of stalks and number of days in August to tasseling and silking. The deviating plants are less than half as productive of grain as the normal line. The reduction of height of stalks is three times the significant difference, and the plants are nine days later in shedding pollen and seven days later in the emergence of pistils.

The two reciprocal crosses are closely alike. The mean of the two first generation crosses exceeds the larger parent by 22 percent in yield of grain, by nine percent in height of stalk, and is three days later in tasseling and two days later in silking than the normal parent, but is two days earlier than the parental mean.

At the time these crosses were made in 1943 the lines that were homozygous for one character only were not recognized. Crosses were made between the normal lines and progenies homozygous for either pale top or crooked stalk and segregating for the other character. These crosses were also grown in the replicated test, but to avoid unnecessary confusion, results are not reported in table 4. The results are the same, within the limits of sampling error, as the crosses with the lines homozygous for both characters. The individual plants in these segregating progenies used for crossing could have been homozygous normal, homozygous recessive, or heterozygous for one of the two characters. From these results it is not possible to say which of the two mutant genes is giving the heterotic effect. Further information on this point is being obtained. From the evidence at hand both are equally effective, but not cumulative in their action. Possibly some other change associated with this variable condition is responsible for the stimulating effect. If so and it is separable from the visible effect, then it may be possible to recover the visible recessive characters from the crosses free from any action on heterosis.

BLOTCHED LEAF

In a long-inbred strain of Connecticut Leaming corn one plant was noted in 1939 that was taller and darker green than the other plants in the same strain growing in the same and adjacent rows. It was not large enough to be a typically outcrossed plant which are found in small numbers in spite of all precautions to guard against contaminations of this kind in the process of hand pollination. When such outcrosses do occur in inbred lines of corn, the resulting heterosis and alteration in plant characters is so marked that there is seldom any doubt as to their nature. In this case there was uncertainty at the time as to whether this plant was an outcross or not.

The inbred line (C14), in which it was found, has many characteristic details of tassel, leaf, stalk, and ear characters. The deviating plant had all of the details of the original line except that it did not show the blotched chlorophyll characteristic of this line. Many inbred lines of corn show chlorophyll variations that are expressed in the later part of the growing season by yellow-

ish dots or blotches of varying size and outline. In this line these lighter colored spots are large and irregular in size and numerous. This condition seems to be a form of premature chlorophyll disintegration.

This line also has much aborted pollen and poorly filled ears due to a condition of asynapsis found in many inbred strains. The self-fertilized ear on this outstanding plant was larger and better filled than any ears previously obtained from these plants. The rows of grain were straight and well filled, and the kernels were brighter in color. Each seed also had a small reddish streak of pericarp color, a condition that had never been noted in this line nor exactly in the same condition in any other line.

The offspring grown from the self-fertilized seed from this more vigorous plant were somewhat variable, but all plants were taller, greener, and more productive than plants of the original line. Numerous progenies were grown for several generations. All returned to the level of vigor of the original line or below.

TABLE 5

A comparison of the blotched leaf variation with the normal line (C14) from which it originated and the first generation hybrid between the normal and mutant lines.

DESIGNATION OF LINE	WEIGHT OF EARS PER PLOT	HEIGHT OF STALK	DATE OF TASSELING	DATE OF SILKING
Normal selfed	1077	70.6	2	4
Normal×normal	1193	73.6	2	4
Blotched	679	73.8	4	4
Blotched×normal	1300	78.2	3	3
Mean, normal and blotched parents	878	72.2	3	4
F_1 − parental mean	422	6.0	0	−1
F_1 − larger or earlier parent	223	4.4	1	−1
Significant difference	207*	4.0		
Percentage increase over larger parent	21	6		

* On .05 level, all other significant differences on .01 level.

There was considerable variation in height of plant and segregation in the amount of chlorophyll blotching in the leaves and in color on the glumes of the tassel, on the internodes and leaf sheaths. Intercrosses between these deviating lines and the original normal line showed clear segregation in glume base color, but other segregations were obscure. After four generations of self-fertilization from the original deviating plant, one line was selected as differing the most from the normal type. The plants are now slightly taller, more heavily blotched, have no glume base color in the tassels, less color on the leaf sheaths and internodes, and are appreciably less productive of grain as shown in table 5. They average two days later in shedding pollen, but the pistillate flowers appear at the same time.

It is possible that the original deviating plant resulted from a chance outcross with a related backcrossed line that was growing in an adjoining row.

The peculiar pericarp color cannot be accounted for, and this coloration never reappeared in any of the progenies grown from this individual. None of the offspring retained the more vigorous growth or greener chlorophyll color, although this condition was especially selected for. Whether this variation originated by mutation or by crossing with a related line, the differences are small.

TABLE 6

A comparison of the late flowering variation with the normal line (C14) from which it originated and the first generation hybrid between the normal and mutant lines.

DESIGNATION OF LINE	WEIGHT OF EARS PER PLOT	HEIGHT OF STALK	DATE OF TASSELING	DATE OF SILKING
Normal selfed	1077	70.6	2	4
Normal×normal	1193	73.6	2	4
Late	530	73.4	5	8
Late×normal	1121	73.7	3	5
Normal×late	1106	73.3	3	4
Mean, normal and late parents	804	72.0	4	6
Mean, F_1	1114	73.5	3	5
F_1 mean−parental mean	310	1.5	−1	−1
F_1 mean−larger or earlier parent	37	.1	1	1
Significant difference	283	4.0		
Percentage increase over larger parent	3	0.1		

From 15 to 20 progenies of the normal C14 line have been grown every year since this deviating individual appeared and have been examined minutely during the entire season. No other variations of any kind have been observed except the late flowering line described below. Intercrosses between these normal lines have been made without any change in growth or productiveness. The results are given in table 5. Normal×normal is the same as normal selfed in weight of ears, height of stalk, and time of flowering. But the cross of blotched×normal is significantly more productive, 21 percent, than the normal more productive parent and taller, 6 percent, than the taller blotched parent and earlier in silking by one day than either parental line.

LATE FLOWERING

The same progeny of the C14 inbred grown in 1939 that produced the tall vigorous plant that later resulted in the blotched leaf variation also produced two plants that were somewhat shorter and later in flowering. These were self-fertilized and grown separately the following year. Late flowering plants again appeared in both progenies. In 1942, after three generations of further self-fertilization, the late flowering condition was established as a uniform characteristic, three days later than the normal line in tasseling and four days later in silking as shown in table 6. Plants of the late line and the normal line in replicated plantings were measured for height during the entire growing season of 1942. Throughout the season measurements were made to the tip of the

tallest leaf or the tip of the tassel, whichever was taller, and the results in the form of growth curves are given in figure 4. The late flowering plants are slower in growth throughout the season. When the normal plants complete their height growth, the late plants continue until the end of the growing season. If the season is long enough, as in 1944 when the results in table 6 were obtained, they may eventually reach the same height.

When measured in 1944, the yield of the late line was less than half of the

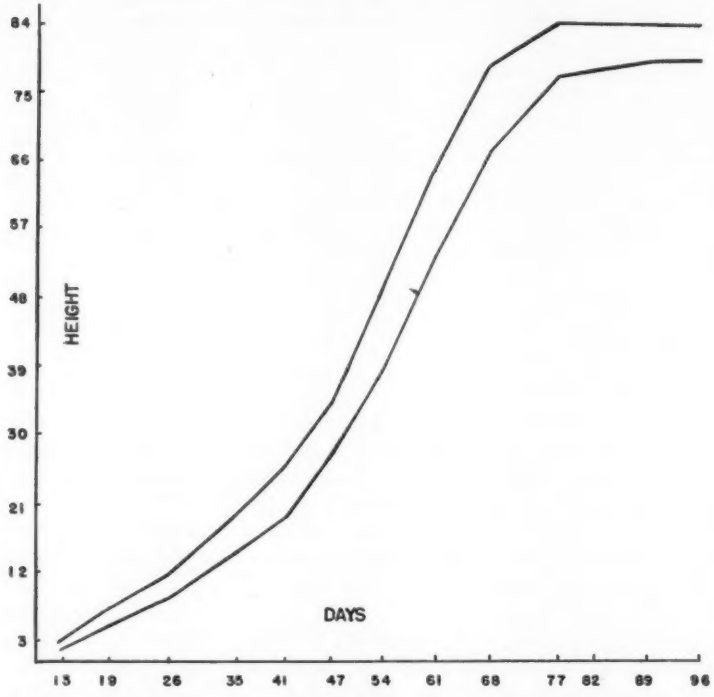

FIGURE 4.—Growth curves of the normal C14 inbred (above), and the late flowering strain.

normal line. In this very dry season any delay in development resulted in a severe reduction in yield, although the late plants were slightly, but not significantly taller. The late plants and crosses with normal were grown in the same test as the blotched leaf variation, since they both originated from the same line. Reciprocal crosses between the late and normal lines agree closely in all measurable characters. The mean of these two first generation hybrids does not excel the normal higher-yielding parent in production of grain. But considering the great differences shown by the two parents, the significant increase over the parental mean indicates at least complete dominance. The hybrid

plants are also as tall as either parent and slightly earlier than the parental mean in time of flowering.

SUMMARY OF FIRST GENERATION CROSSES

In table 7 the results of all five crosses are brought together. The increases in yield of grain and in height of stalk are given in percentage above the higher yielding or taller parent in each case. The time of flowering of the crosses is compared to the earlier parent or the mean of the parents. The heterotic effect is clear in all cases with the possible exception of the late flowering character. But even in this case, the fact that the crossed plants made the same amount of growth in less time than the parental mean indicates a tendency in the direction of heterosis.

TABLE 7

Summary of comparisons of the F_1 with their parental lines.

DESIGNATION OF LINE	PERCENTAGE INCREASE OF F_1 OVER LARGER PARENT		DATE OF FLOWERING	
	YIELD	HEIGHT	TASSEL	SILK
Narrow leaf	104	5	= Early parent	< Mean
Dwarf plant	98	3	< Early parent	< Early parent
Pale and crooked	22	9	< Mean	< Mean
Blotched leaf	21	6	= Mean	< Early parent
Late flowering	3	0	< Mean	< Mean

OUTCROSSES TO UNRELATED LINES

Both normal and deviating lines in each case were crossed with normal unrelated lines with which the normal line had given large increases in yield. The larger growth of these outcrosses, compared to the related crosses, drew so heavily on the limited moisture in an unusually dry season that the results of the test are inconclusive. The late and dwarf deviating lines used as one parent yielded more than the normal line combined with the same unrelated inbred. The pale leaf, crooked stalk, and the narrow leaf deviations yielded less than the normal line in similar crosses. The blotched leaf line was not tested. None of the differences is significant, and further results are needed to clarify this point. It is not expected that in these unrelated crosses where so many differences are involved, the changes involved in these deviating lines could have much effect. The fact that they do not reduce yields is important.

DEGENERATE CHANGES IN OTHER MATERIAL

Variations that reduce the amount or rate of growth or decrease the ability of the organism to reproduce itself have been reported in nearly all forms of life. Most of these alterations occur in such heterogeneous stocks that it is not known whether they are single or multiple gene changes and the effects of these altered alleles have not usually been compared, free from the effect of

other genic recombination, in crosses with the normal individuals from which they arose. One case in tobacco has been studied in detail and reported previously (JONES 1921). This is the change from the normal determinate type to the indeterminate type that never flowers in the usual outdoor season, but will flower and produce seed in a shortened period of daylight as when grown in the greenhouse during the winter. This variation, on good evidence, is a single gene change from a dominant to a recessive condition. The mutant has been noted under field conditions in many varieties of cultivated tobacco. It has occurred in other plants and also in maize.

The deviating line is unable to reproduce itself at all in the environment in which it regularly occurs. Yet in the heterozygous condition this allele in Nicotiana increases the number of leaves, height of stalk, and total number of seeds produced. Rate of growth is not accelerated, but total amount of growth is augmented due to an extension of the growing period.

ROBBINS (1940, 1941) has shown that extracts from the seeds of hybrid maize promote a greater amount of early growth of test fungi than similar extracts from inbred parents. These results were obtained only when other essential growth substances were present in the media. Varieties of tomatoes respond differently (ROBBINS 1941) to various growth promoting substances. Their hybrids combine the ability of both parents in this respect. BEADLE and TATUM (1941) obtained induced mutant strains of fungi lacking the ability to synthesize certain essential growth substances. Their results were interpreted as showing that a "given gene has a single primary action." But they did find a mutant strain that was able to grow on a medium containing yeast extract, but unable to grow on any of the synthetic media so far tested. This indicates either some unknown growth factor present in the yeast or that the mutant strain lacks the ability to synthesize more than one known substance.

DISCUSSION

The results reported here are surprising since numerous investigations have shown no appreciable effect of genes in the heterozygous condition. JONES and MANGELSDORF (1925) compared the yield of 25 inbred progenies segregating for various recessive abnormalities with an equal number of similar progenies free from such segregations. The yield was practically identical. MANGELSDORF (1926, 1928) obtained measurements for time of flowering, length and weight of ears, and height of plant in maize heterozygous for a single lethal seed factor in comparison with homozygous normal and found no superiority of the heterozygous plants. GARBER and ROWLEY (1927) reported that plants heterozygous for a defective endosperm gene yielded significantly less than normal plants of a similar composition without the recessive allele.

WENTZ and STEWART (1927) studied a deleterious recessive gene in soybeans. Heterozygous plants were nearly equal in yield to homozygous normals but clearly showed no heterosis. KARPER (1930) compared sorghum plants that were heterozygous for a lethal chlorophyll gene with homozygous plants. One normal allele was apparently as effective as two in producing normal chloro-

phyll. The heterozygotes were slightly more vigorous and productive but not significantly so. ROBERTSON (1932) found no detrimental effect of a single seedling lethal factor in the heterozygous condition in the development of barley.

In view of these findings it is obvious that differences depend upon the nature of the gene itself. It is certainly not the result of heterozygosity itself. The investigations noted above were mostly with lethal or nearly lethal factors. The genes described here are apparently of a different nature. While they are all unfavorable to the plants, they reduce size and reproductive ability only moderately.

Variations in both plants and animals, favorable to the organism in some respects, that have arisen under known conditions are very few. Most of the cases on record are due to gene recombination rather than mutation. DOBZHANSKY, HOLZ, and SPASSKY (1942) report the isolation of genes in Drosophila that increase the reproductive capacity of the organism. These variations originated under natural conditions, but they occurred some time before they were isolated, and little is known about the recombination which may have taken place before their uncovery. Their beneficial effect may be due to mutant alleles working in conjunction with other factors, as in the cases reported here. A shifting of genic materials, favored by natural selection, could bring about recombination within the chromosomes such that it could later be isolated in a homozygous condition. Evidence for such intra-chromosomal recombination has been presented by GOLDSCHMIDT (1945).

MATHER (1941) visualizes a condition of enforced heterozygosity, especially in regions near the centromere, in which rare crossing over releases extensive genetic variability. Heterosis automatically selects for a condition of enforced heterozygosity, and heterotic genes tend to accumulate by natural selection. In the five deviating lines reported here, involving at least six allelic differences, four of the differences occurred in two lines. Three other differences also appeared later in one of these lines which have not yet been studied. This provides good evidence that numerous changes occur at or near the same time. But if these variations are segregations from an enforced heterozygous heterotic complex, the segregates from the same line should give no more heterosis when recombined than shown by the original line. Actually the heterotic effect resulting from the deviating line crossed back to normal is greater. Whether more than one allelic alteration is involved has no bearing on this interpretation since there is no opportunity to accumulate more different dominant effects than are present in either parent unless a gene has more than a single primary action.

Heterosis could result from a single allelic difference if the change involved more than a single function. It is probable that living organisms are so highly developed and genic action is so delicately balanced that an increase in any physiological function is accomplished at the expense of some other action. The deviating lines that grow less well than their parents may have gained in some important function, but with a loss in some other effect. The normal

equilibrium of total genic action has been upset. This is restored in the hybrid, since the normal parent supplies what the mutant line lacks and the mutant adds whatever it has gained in efficiency. This may be interpreted on the basis of competition for substrate materials. The mutant line, as a hypothetical example, may be able to use more of the basic material in the formation of an intermediate product but is unable to carry this reaction on to the full amount of final product that the original allele can manufacture. According to this assumption, there is a pooling of hereditary resources in a heterozygous condition involving a single allelic difference as well as when more differences are involved.

The manifold effect of genes has been studied by DOBZHANSKY (1927) following up earlier investigations by MORGAN (1919), JOHANNSEN (1923), PLATE (1910, 1913), and others. The term pleiotropism has been used to describe the action of one gene . . . "on the characters of different parts of the body which are often without a clear functional connection with one another" (DOBZHANSKY 1927, p. 331).

SYNERGESIS AND HETEROSIS

A stimulus arising from a heterozygous condition was originally postulated by EAST(1909), EAST and HAYES (1912), A. F. SHULL (1912), G. H. SHULL (1914). This conception was extended by RASMUSSON (1934) and by EAST (1936), as an interaction between alleles. The similarity between such an effect and synergesis is apparent. Metallic alloys are familiar examples of substances which in combination have properties that surpass in some respects either substance alone. Pathologists and entomologists give numerous examples of materials that are more or less toxic to organisms when acting in combination. Toxicity varies with the proportions of the ingredients.

As far as it applies to heterosis, the assumption of a synergetic interaction between alleles is merely a restatement of the problem and up to the present time discussion has been largely fruitless. Further evidence is needed to show the nature of the changes resulting in a direct loss to the individual, but ultimately a possible gain to later generations. Can the effect in heterozygous union be reconstituted in a homozygous condition? From the limited evidence presented here it appears that progressive evolution proceeds first by taking a step backward before going forward. This makes somewhat more understandable the reason why favorable variations are not more apparent in nature. It also emphasizes the importance of caution in applying any rigorous selective elimination of degenerate individuals either in plant and animal breeding practice or in eugenic procedure.

SUMMARY

Six recessive variations have appeared spontaneously in five inbred lines of maize. All of these reduce the amount or rate of growth in some respect and would be classed as degenerative changes.

The evidence obtained so far indicates that they differ from the normal homozygous line in which they originated by single allelic alterations.

When these reduced mutant lines are crossed with the normal lines from which they originate, they show a surprisingly large amount of heterosis. This varies from 3 to 104 percent in yield of grain above the more productive parent and from 0 to 9 percent in height of stalk above the taller parent in each case. This greater growth is made in every case in less time than the parental mean and in two cases in less time than the earlier parent.

In one line five variations occurred at about the same time. Three of these have not been studied and are not included. In another line two variations also appeared simultaneously. The loci involved have not been located, but two of them appear to be independent.

These degenerate changes at least do not reduce the yield of their offspring in crosses to unrelated lines and from the evidence in other maize material may actually increase yields.

Heterosis is interpreted as an accumulative effect of favorable heredity from both parents. This results even when only single allelic differences are involved provided genes have multiple effects.

ACKNOWLEDGMENTS

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A CASE OF NEIGHBORING LOCI WITH SIMILAR EFFECTS

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INTRODUCTION

IT HAS been assumed, more or less as a matter of course, that the hereditary unit in the chromosome which is not broken by crossing over—that is, the gene—also functions as a physiological unit in development. Such an assumption is indeed required by most of the evidence upon which rests the basic postulate of genetics—the occurrence of sharp segregation of alleles—since the segregating units are recognized by their phenotypic effects and the different allelic conditions of the unit of segregation generally retain a certain unity and relatedness in their effects on development.

There is, moreover, the fact which emerged when the first "maps" of the Drosophila chromosomes appeared, and which is generally true in linkage maps in other animals and plants, that gene loci are scattered through the chromosomes without regard to developmental effect. Loci which are so close as to be seldom separated by crossing over do not necessarily resemble each other in their effects, while those with chief effects on very different structures or functions may occur near together or far apart. The differential physiological effect of each allele appears to derive from its own locus, dependent, of course, on cooperating influences from other loci and from the environment. This statement remains generally true in spite of the proof that in a few cases the effect of a gene is changed when its position is changed. The observed position effects in Drosophila represent changes in the magnitude of an effect, like those associated with changes at the same locus; they do not alter the fact of qualitative dissimilarity between neighboring loci.

A third fact of interest is that what seems to be the same differential effect on development may be brought about by any one of several distinct loci in different parts of the chromosome complement. When these are widely separated, it can be supposed that each represents the same type of change in an element that is repeated in several parts of the chromatin. In fact the correlation between repeated chromosomes (polyploidy) and repeated loci (duplicate genes) receives its best interpretation from just such a supposition.

The question has seldom been asked "what meaning is to be attached to such mimic or duplicate genes when they are very near to each other in the chromosome and when their effects are not identical but only very similar?" Such questions present themselves when actual cases of this sort are found, and even though such cases are rare, they suggest hypotheses which call into

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question the universal correspondence between units of crossing over and units of developmental effect.

A preliminary description of such a case in the house mouse has recently been given (DUNN and CASPARI 1942). Five mutations, each affecting the tail and axial skeleton in similar ways, appeared to be located in the same chromosome, very near to each other. Three of them were at different loci separable by crossing over. Two possible explanations of these relationships were suggested. One was that the association of five similar mutations was due to chance —they happened to occur near to each other and happened to resemble each other. The other was that their similarity was due to their proximity—that is, that there was a unit of physiological effect within the chromosome of greater extent than a crossing over unit.

In order to test the first hypothesis (chance), two main questions must be answered. How near are the loci involved, and how many such loci are there in the house mouse? Preliminary studies of crossing over led to an estimate of the likelihood of association of the three loci being due to coincidence as $p = .000008$. The present paper will present the full breeding data obtained on this question and a revised probability estimate which leads to the rejection of the hypothesis of coincidence.

The investigation of the second hypothesis requires first an answer to the question "How alike are the developmental effects of the contiguous loci?" This can be obtained from a comparison of the adult phenotypes of the mutations involved and particularly of the embryological processes through which the phenotypes are reached. Although some preliminary results on these questions have been obtained during the breeding experiments reported herewith, the embryological and anatomical observations are as yet incomplete and will be published separately later.

DESCRIPTION OF THE MUTATIONS

Brachyury and taillessness

Of the five mutations dealt with, three have already been described in detail. These are Brachyury or dominant short tail (T) and the recessives t^0 and t^1, either of which when combined with T (Tt^0 or Tt^1) produce taillessness. The first was described by DOBROVOLSKAIA-ZAVADSKAIA (1934) and CHESLEY (1935), and some details on its expression have been added by GREEN (1936) and DUNN (1942). The other two, taken from lines discovered by DOBROVOLSKAIA and KOBOZIEFF, were studied by CHESLEY and DUNN (1936), DUNN and GLUECKSOHN-SCHOENHEIMER (1939) and GLUECKSOHN-SCHOENHEIMER (1938) as reviewed by DUNN (1941). The essential points are that T usually behaves as a dominant, its principal effect in heterozygous condition being to shorten the tail. Its expression is subject to marked influence by a number of genetic factors, some of which enhance its effect, $T +$ being nearly tailless; others of which tend to suppress the expression of T,$T +$ being nearly normal. The form of the tail is also subject to modification, ankyloses or fusions between neigh-

boring vertebrae, contortions, angular kinks and similar irregularities occurring with some frequency in different stocks.

The most constant feature is shortness of the tail, and this phenotype is reached as a result of the death and dissolution of the distal part of the tail which was fully present in the embryo. This degenerative change is connected with the absence of the notochord which stops short in the tail or, as in the tailless forms, at the end of the sacrum, the parts lacking notochord undergoing histolysis. Homozygotes (*TT*) lack normal notochord and allantois and regularly die at about 11 days after fertilization, while t^0t^0 embryos die during gastrulation without ever forming mesoderm. The effects of t^1t^1 are not known, since these embryos die before implantation.

Fused

The dominant mutation Fused was first described by REED (1937). He found it to have quite variable effects on the tail, many of these, such as shortness or absence, presence of asymmetrical fusions of vertebrae with thickenings, kinks and contortions, resembling the variations found in the Brachyury mutant. Unlike Brachy, however, it proved to be viable in the homozygous condition, since REED found a few adult homozygotes, and it produces certain effects not found in Brachyury—namely, frequent fusions of ribs and of thoracic and lumbar vertebrae and occasional bifurcations of the tail. Some animals heterozygous for Fused presented an entirely normal appearance and could be detected only by progeny tests. REED reported also that such phenotypically normal animals ("normal overlaps") were much more frequent in outcrosses of Fused females than of Fused males, a circumstance not observed with Brachy or with any other mutation in the mouse. Because of the absence of proved crossovers between Fused and Brachy, REED supposed that Fused might be a less extreme allele of Brachy.

In addition to these, we have noted other effects of Fused. The most striking of these is a type of choreic behavior like that of the Japanese waltzing mouse but more variable and chaotic. This is usually accompanied by deafness. These abnormalities are found frequently in both heterozygotes and homozygotes but have not become constant under inbreeding. Rarely in Fused stocks anaemic young are found at birth. Neither waltzing, deafness, nor anaemia have ever been found in our extensive experience with Brachyury.

In our experience the viability of Fused homozygotes is very poor, the young *Fu Fu* dying shortly after birth, most of them with pronounced urogenital and gut abnormalities which will be described elsewhere.

No descriptions of the embryological manifestations of Fused have been published beyond the statement of REED (1937) that the first observable abnormalities in Fused embryos are poor alignment of notochord and curves and angles of the neural folds and that its embryological effects resemble those of Brachyury. An embryological study of Fused now in progress suggests further differences between Fused and Brachyury.

Kink

In 1937 a mutation like Fused was found by MR. S. P. HOLMAN and was studied and described as "Kinky tail" by CASPARI and DAVID (1940). Its manifestations in heterozygotes have since been more carefully studied by CASPARI (unpublished manuscript). The phenotypic effects of Kink proved to be very similar to those of Fused: it is dominant, usually shows reduction in the number of tail vertebrae, with abnormal fusions and ankyloses between neighboring vertebrae which cause angular kinks or stiff segments and occasionally bifurcations of the tail. Like Fused also, Kink-tailed animals frequently show disturbed behavior of the choreic or waltzing type, and many of them are deaf. All three manifestations (Kink tail, disturbed behavior, and deafness) appear to be effects of the one mutation and have not been separated from it. All three are also variable and show different frequencies and degrees of expression in different inbred strains. The most reliable indication of *Ki* is the tail abnormality which is present in 95 percent of *Ki* heterozygotes. Occasional animals show no external signs of fused vertebrae, but when the skeletons of these are stained and cleared for study, all show abnormal or reduced vertebrae or fusions. Tail length varies from tailless (rare) to nearly normal length; the number of kinks and the form of the tail is likewise variable. Length and form of the kink tails tend to become more constant in a stock after inbreeding.

Deafness was found in 31 percent of 925 kink-tailed animals of five different inbred strains. The strain frequency varied from 5 to 57 percent. Disturbed behavior was noted in 24 percent of 1040 kink-tailed animals of the same inbred strains as above. The frequency differed in different strains and could be increased by selection, showing that other factors besides *Ki* are concerned. Nearly always disturbed behavior is accompanied by deafness, although an occasional animal with abnormal behavior fails to show the external tail abnormality. It is likely that behavior and deafness are influenced by some of the same modifying factors. Although the deafness and disturbed behavior which accompanies Fused have not been carefully studied, it is probable that they closely resemble those connected with Kink.

The Kink mutation is distinguishable from Fused by its lethal effect. Kink homozygotes regularly die at about the ninth day after fertilization, whereas most Fused homozygotes survive until birth. *Ki* nearly always manifests itself in heterozygotes, whereas *Fu* heterozygotes often show no external tail abnormalities; and *Ki* males and females have similar offspring, whereas Fused females have phenotypically Fused offspring with less than normal frequency (REED 1937). Finally, *Ki* was shown by crossing over tests to be distinct from *Fu*, although closely linked with it (DUNN and CASPARI 1942).

All these facts have been confirmed by the further observations reported in this paper. In our experience, Kink and Fused animals from unselected stocks are phenotypically indistinguishable. Either one can be distinguished from Brachy with certainty only when waltzing behavior is present, since this never appears as part of the Brachy phenotype. Experiments now in progress indi-

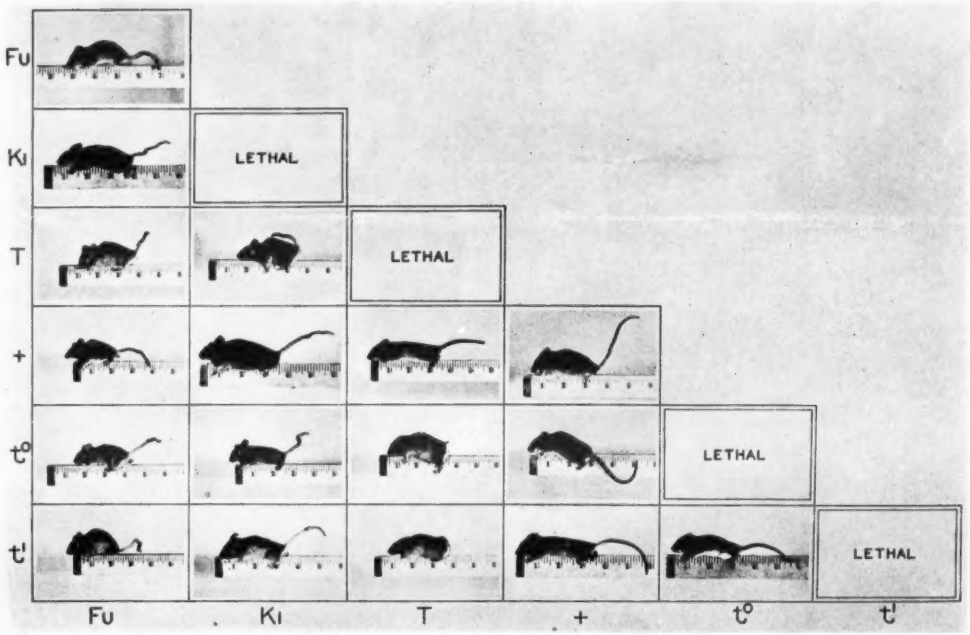

FIGURE 1.—Photographs of mice containing combinations of the neighboring mutations Fused (*Fu*), Kink (*Ki*), Brachy (*T*), t^0 and t^1. Gene received from father is shown at left, from mother below.

cate that partially isogenic stocks of *Ki*/+, *T*/+, and *Fu*/+ obtained by 16, 15, and 11 generations of backcrossing to a Bagg albino strain may show consistent differences in tail length, *T*/+ being shorter than *Ki*/+ or *Fu*/+, both of the latter being alike and of nearly normal length with few kinks.

EFFECTS OF THE MUTATIONS IN COMBINATION

When the individual mutations are combined with each other, an interesting set of relationships appears, as shown in figure 1. The specimens illustrated are typical or average, since Fused, Kink and Brachy are all quite variable and lines of these which are isogenic with each other have not been obtained.

Only one homozygous combination is viable—namely *Fu*/*Fu*, and this infrequently survives to reproduce. *Fu*/*Fu* usually has a shorter and more deformed tail than *Fu*/+, as REED noted, but some *Fu* homozygotes have tails like *Fu*/+.

The comparison of heterozygous combinations shows that the three dominants *Fu*, *Ki*, *T* do not influence each other appreciably. There is no marked cumulative effect of two mutations which have similar individual effects. It has been found, however, that in certain families derived from a crossover individual, *Ki T*/++, tailless animals occur. This probably depends on a special factor rather than on a cumulative effect of *Ki* and *T* when in the same chromosome, since *Ki T*/++ is often indistinguishable from *Ki*/*T* or *Ki*/+.

Neither *Ki* or *Fu* is markedly influenced by either of the recessives t^0 or t^1, whereas *T* is strikingly modified, *T*/t^0 and *T*/t^1 usually being entirely tailless. This difference is sufficient, in progeny tests, to distinguish *Ki* and *Fu* on the one hand from *T* on the other. We have found no difference in effect on the tail between t^0 and t^1 when combined with *T*. Although t^0/t^1 has a normal tail, these two mutations do interact to produce male sterility always, and head and eye abnormalities frequently. Such abnormal animals usually die as embryos (DUNN and GLUECKSOHN-SCHOENHEIMER 1943), but occasionally one survives, as for example, the animal in the lower right corner of figure 1 which has a microphthalmic left eye.

A few triple combinations have been observed and will be described in more detail elsewhere. *Ki T*/t^0 and *Ki T*/t^1 have a more extreme phenotype than *T*/t^0 or *T*/t^1 and show evidence of a cumulative effect in the greater frequency of malformations of the anus and urinary system. *Ki T*/*Fu* may be entirely tailless, but since *Ki T*/++ may also be tailless, no conclusions concerning cumulative effect can be drawn.

In respect of interaction effects, therefore, two groups of mutations can be recognized: (1) *Fu* and *Ki*—entirely indistinguishable from each other, except in the lethality of *Ki Ki*, and showing no marked interaction with each other or with the other three mutations; (2) *T*, t^0, and t^1 which mutually modify each other and do not share the waltzing, deafness, or duplicity (bifurcation) peculiarities of *Fu* or *Ki*.

All five mutations have this in common, that they alter the development of the spinal column in similar ways and give rise to similar phenotypes. The im-

portant question is thus raised what relation exists between their resemblances and differences and their locations in the chromosome.

RECOMBINATION FROM *Fu* +/+ *T*

In a first report we estimated that about two percent recombination occurred between *Fu* and *T*. This was based on the proof that four offspring (in a total of 400) from *Fu* +/+ *T* were crossovers of the ++ type, constituting half of the recombinations. These observations have been extended and confirmed.

The results of testing *Fu* +/+ *T* are shown in tables 1 and 2. The cross of *Fu* +/+ *T* males by normal females produces chiefly animals with Fused or Brachy tails. Two types of exceptions appeared. The first type was tailless and may represent either extreme expression of Fused or Brachy or possibly the crossover type *Fu T*/+ +. All of these died shortly after birth so that none could be tested. The second type was more frequent and had a normal tail. These could be either *Fu*/+ or *T*/+ which failed to manifest the mutant effect (normal overlap) or crossovers of the ++ type. These exceptions are

TABLE 1

Tests of Fu+/+T×++.

Fu+/+T PARENT	*Fu* OR *T*	TAILLESS	OFFSPRING NORMAL				CROSSOVERS	TOTAL
			TESTED *Fu+*	TESTED ++	NOT TESTED	TOTAL NORMAL		
Males	472	8	10	10	3	23	10	503
Females	111		10		16	26	—	137

TABLE 2

Tests of Fu+/+T ♂♂ by t^0t^1 ♀♀.

Fu (*Fu*/t^n)	TAILLESS T/t^n	NORMAL-TAILED TESTED *Fu*/t^n	TESTED +/t^n	NOT TESTED	TOTAL	CROSSOVERS	NON CROSSOVERS	TOTAL
74	75	1	4		5	4	150	154

fully viable and fertile and can be readily progeny-tested by mating to wild type (++). When this was done, ten of these exceptions proved to be *Fu*/+, while ten failed to produce mutant offspring in progenies of from 26 to 50, usually 35 (table 3). The latter are apparently ++ and represent half of the total crossovers. Their frequency should thus provide a good measure of the crossover value *Fu-T*. From *Fu* +/+ *T* males, the proved crossovers were ten out of 503 or two percent, leading to a crossing over estimate of four percent.

The same males were tested by t^0/t^1 females (table 2). It has been shown

that t^0 and t^1 do not cross over, hence every gamete of such females carries either t^0 or t^1. The non-crossover progeny from such a cross should thus be Fu/t^n and T/t^n. The latter are tailless; the former generally Fused. Crossovers detectable would be $+/t^n$ with normal tails. Actually five out of 154 progeny were normal, and of these, four or 2.6 percent were crossovers producing, respectively, 43, 38, 51, and 45 normal progeny while one was an overlap. The results show that the frequencies of the two non-crossover gametes *Fu* and *T* are equal, since equal numbers of $Fu(Fu/t^n)$ and tailless (T/t^n) offspring were found.

From *Fu* +/+ *T* females, a high frequency of normal-tailed exceptions was obtained (26 out of 136), but upon progeny-testing ten of these, all proved to be *Fu*/+. The high frequency with which *Fu* failed to manifest itself in the prog-

TABLE 3

Progeny tests by ++ of exceptional normal-tailed offspring from Fu+/+T♂×++♀ which gave only normal progeny.

ANIMAL TESTED	NORMAL PROGENY
♀ 8256	26
♂ 8397	37
♂ 8151	37
♀ 8530	49
♂ 8544	33
♂ 9925	35
♀ 10137	42
♂ 10144	42
♂ 10145	50
♀ 10205	47

eny of *Fu* females was not unexpected, since REED (1937) had noted this fact; but failure to find a single crossover among ten tested was surprising. If crossing over in males and females is equally frequent, two crossovers would be expected in the sample examined. The deviation of the actual from the expected, in a total of 121, is not significant (p=.09); hence the result may be due to chance rather than to failure of crossing over in the female. Nevertheless, it seems safer to omit the offspring of *Fu* +/+ *T* females in reaching an estimate of the amount of crossing over between *Fu* and *T*. The totals are thus 14 detected crossovers out of 657, or 2.13 percent, representing a crossing over percentage of 4.26.

RECOMBINATION FROM *Ki* +/+ *T*

Our first estimate of about two percent of crossing over between the loci of *T* and *Ki* has not been greatly altered by additional evidence. The chief test cross (*Ki* +/+ *T* × ++) was carried out in both laboratories (Lafayette and Columbia) with stocks of different derivation. The method was to detect one type of crossover—that is, ++ (normal-tailed), since the other type expected (*Ki T*/+ +) could not ordinarily be distinguished from the non-cross-

over types *Ki* and *T*. In addition, *Ki* +/+ *T* males were tested by t^0/t^1 females. In this cross, the non-crossover gametes *Ki* and *T* lead to sharply different phenotypes, Ki/t^n having a Kinked tail, T/t^n being entirely tailless. This permits an estimate of the relative viabilities of the two non-crossover types .The data show these to be about equal. In all cases, suspected crossovers—that is, progeny with normal tails—were progeny-tested by mating with animals from normal stock, and only those which produced 30 or more (usually over 40) normal progeny were accepted as valid crossovers. This precaution is required by the fact that rarely *Ki*/+ fails to show the Kink phenotype and without progeny tests such normal-appearing animals would be counted as ++ crossovers.

TABLE 4

Tests of recombination in males and females of genotype Ki +/+ T.

Ki+/+*T* PARENT	*Ki* OR *T*	TAILLESS	NORMAL-TAILED				CROSSOVERS	TOTAL CLASSIFIED
			TESTED *Ki*+	TESTED ++	NOT TESTED	TOTAL NORMAL		
♂♂×++(C)	521	2	—	4	—	4	4	525*
♂♂×++(L)	326	5	2	6	2	10	6	334*
♀♀×++(C)	218	2	1	8	3	12	8	227*
♀♀×++(L)	304	9	3	8	2	13	8	315*
♂♂×t^0t^1 (C)	135	127	3	4†	2	9	4	269
Totals	504	145	9	30	9	48	30	1670*

* Untested normals and tailless could not be classified as crossovers or non-crossovers and have been omitted from the totals.

† Tested = $+/t^n$.

(C) = tested at Columbia; (L) = tested at Lafayette.

The complete data are shown in table 4. There were 30 proved crossovers in a total of 1670, or 1.8 ± .32 percent, leading to an estimate of 3.6 percent crossing over. This must be a minimum estimate, since out of the 48 normal-tailed suspected crossovers, the progeny tests of nine were not conclusive because of sterility, early death, or loss from other causes. Of those tested, about three-fourths (30 out of 39) turned out to be crossovers, while about a quarter proved to be normal overlaps. It is likely therefore that six or seven of the untested animals were also crossovers, which would raise the total number to about 36 out of 1670 and the estimated crossing over percentage to 4.3.

Crossing over occurred in both sexes. From heterozygous males the frequency of detected crossovers was 14/1128 or 1.24 ± .33 percent; from females 16/542 or 2.95 ± .73. The difference, 1.71 ± .8 percent, while barely significant, (p = .04) is in the same direction as sexual differences in crossing over previously reported for the house mouse.

The results obtained in the two laboratories are comparable. The crossovers detected at Lafayette from tests by ++ were 14/649 or 2.15 ± .57 percent; at Columbia from similar crosses these figures are 12/752 or 1.59 ± .46. The difference, .56 ± .60, is not significant.

RECOMBINATION FROM *Ki T*/+ +

From *Ki* +/+ *T* ♂♂ × ++ at Columbia, two tailless males were found (out of 527 test cross offspring). One of these was abnormal with spina bifida aperta. The other was vigorous and survived (♂ 8756). Suspecting that this might represent the *Ki T*/+ + recombination type, we tested this animal for *T* and for *Ki*. He was first mated to Brachy (*T* +) females which were dissected in the 10th–12th day of pregnancy. Typical *TT* abnormal embryos were found, proving that the father transmitted *T*. Normal females pregnant by the exceptional male yielded embryos with branched and forked tails typical of those found in Kink matings.

This male was then mated simultaneously to ++ and to t^0/t^1 females, and 81 and 95 offspring were recorded at birth, as shown in table 5.

TABLE 5

Offspring from tailless ♂ (from Ki/T×++) tested by normal (++) and by t^0/t_1 females.

MOTHERS	NORMAL	KINK	TAILLESS	TOTAL
+/+	33	24	24	81
t^0/t^1	52	5	38	95

The first mating, by normal, shows that about half the gametes (48) of the exceptional male transmitted an abnormal tail condition, either Kink or tailless. The appearance of the tail, the expression of waltzing behavior (frequent in Kink, absent in Brachy) and of spina bifida aperta among the progeny indicated that the factor *Ki* was being transmitted. The second experiment confirmed this and showed that *T* was also transmitted, since nearly all the abnormal-tailed offspring were tailless as in T/t^0 or T/t^1.

The results could be accounted for by assuming that the exceptional male was *Ki T*/+ +—that is, a crossover from *Ki* +/+ *T*. The five Kink animals from the cross with t^0/t^1 should therefore represent crossovers *Ki* +/+ t^0. Most of the Kink and tailless animals from the cross with normal should be *Ki T*/+ + like the father.

Progeny tests of 24 offspring from the cross *Ki T*/+ + ♂ × ++ ♀ (table 6) showed that one male (9525) was *Ki* +/+ +, two (9388 and 9227) were probably + *T*/+ +, while the rest were probably *Ki T*/+ +. The tests were made by mating each animal to both +/+ and t^0/t^1 or +/t^0 or +/t^1, as shown in table 6. Those which produced about equal numbers of normal and abnormal-tailed when bred to normal, and equal numbers of normal and tailless when bred to t^0/t^1 were assumed to be *Ki T*/+ +. Those which gave Kink and normal by normal mates and the same by t^0/t^1 were probably *Ki* +/+ +; while those which give Brachy and normal by normal, and normal and tailless by t^0/t^1 should be *T* +/+ +. The last result cannot be distinguished with certainty from the first (*Ki T*/+ + × t^0/t^1) but in large progenies the absence of abnormals, of waltzers, and of forked or Kinked tails among the progeny will

usually decide in favor of T +. The two diagnoses of T +/+ + are not certain, since they were based on tests of females which cannot be tested by t^0/t^1 since t^0/t^1 males are sterile. Both of these females when tested by normal gave equal numbers of offspring with normal and with short tails resembling Brachy; by $+/t^0$, each gave normal, tailless, and Brachy, with no signs of waltzing, Kinked tails, or other abnormalities. Both were thus probably T +/+ +.

The total tested offspring from the exceptional male by normal were thus 21 $Ki\ T$/+ +, one Ki +/+ +, two probably T +/+ +. This would indicate a very high proportion of crossovers, 3/24, but such results cannot be used as a measure of crossing over, because the non-crossover type $Ki\ T$ has two abnormal mutations and is known to exhibit abnormalities such as imperforate anus and spina bifida aperta and to suffer a much heavier postnatal mortality than the crossovers in which the abnormal mutations are present singly.

From the cross of the exceptional male by t^0/t^1 many of the tailless offspring were abnormal at birth, while most of the others died before weaning. We were thus able to test only five tailless animals, all of which were probably $Ki\ T/t^n$. Two kink-tailed progeny (♂ 9714, ♀ 9213) proved to be Ki $+/t^n$ and were thus crossovers as assumed.

Most of the tailless animals from this cross contained three mutations $Ki\ T/t^n$ and owe their abnormalities and poor viability to this condition. We made observations on 84 tailless offspring from $Ki\ T$/+ + × t^0/t^1. Of these only 24 (28 percent) lived to the age of one month; 47 (56 percent) died shortly after birth, and 13 (16 percent) showed imperforate ani at birth and were killed and dissected. All but two of the latter had anal and urogenital abnormalities which would have prevented their survival. Of the 84 born, no less than 34 had severe lesions of the spina bifida aperta type. It is obvious that Ki and T with either t^0 or t^1 tend to produce a very abnormal phenotype. Some $Ki\ T/t^n$ animals survive and breed, however, and it has been possible to test ten such males for crossing over between Ki and T.

The above results demonstrate that the exceptional male had Ki and T on the same chromosome, and that more than half of his offspring received this chromosome. In a few cases, however, crossing over again restored the original combinations Ki/+ and T/+. The frequency of crossing over will be discussed below.

Tests of offspring from the exceptional male also showed that the presence of Ki and T on the same chromosome does not necessarily produce a more extreme phenotype than Ki +/+ T, as might have been suspected from the tailless condition of the original exception. Thus of 21 offspring shown to be $Ki\ T$/+ +, ten had Kink tails from $\frac{1}{8}$ to $\frac{3}{4}$ of the normal length, while 11 were tailless. The two classes probably intergraded. Five of these F_1 tailless males when bred to normal gave 81 normal, 73 Kink, and eight tailless; while four of the F_1 Kink-tailed males bred to similar normals gave 66 normal, 62 Kink, and nine tailless. Thus tailless and Kink-tailed males had similar progenies. Taillessness was so rare in the combination Ki +/+ T as to suggest that Ki

TABLE 6

Tests of exceptional male 8756 (Ki T/++) and of his descendants from crosses with normal (++).

TEST ANIMAL ♂	OFFSPRING FROM CROSS WITH ++			FROM CROSS WITH +/l^0			FROM CROSS WITH l^0/l^1			ASSUMED GENOTYPE
	NORMAL	KINK	TAIL-LESS	NORMAL	KINK	TAIL-LESS	NORMAL	KINK	TAIL-LESS	
♂ 8756 tailless	33	24	24	20	8	16	52	4^{+1}	38	*Ki T*/++
F_1♂ 9121 "	14	11	—	—	—	—	16		9	*Ki T*/++
9172 Kink	31	19	—	12	2	6	37	2	35	"
9173 tailless		5	—	3	—	3	3		7	"
9174 "	18	20	—	15	5	14	17	1	21	"
9292 Kink	12	13	1	34	4	11	20	—	24	"
9293 tailless	13	13	3	7	—	8	3		2	"
9296 "	12	4	2	6	3	5	4		4	"
9386 "							5		4	"
9387 Kink	8	7	8	18	6	6	—		—	"
9418 "	10	16		15	8	9	32	2	29	"
9526 tailless	17	14	1	19	1	13	—	—	—	"
9527 "	7	6	2	8	2	6	5		8	"
	175	152	41	157	39	97	194	9	181	
F_1♂ 9525 Kink	5	7					19	15	1	*Ki* +/++
F_1♀ 9225 Kink*	1	6		8	1	5				*Ki T*/++
9227 "	8	6		13	10†	5				+*T*/++(?)
9228 "	10	8	2	2	1	2				
9229 "	10	8	1	11	5	3				
9230 "	11	8	3	4	1	4				
9294 tailless	1	2	5	2	3	2				
9295 "	2	2	4	4	1	2				
9321 Kink				3		4				*Ki T*/++
9388 Brachy	8	8		14	6†	14				+*T*/++(?)
9528 tailless	1		1*							
9417 Kink	3	2		10	1	6				
	—	—	—	—	—	—				

* Waltzing.

† Brachy in appearance.

and *T* do not interact cumulatively. Taillessness is much more common in the combination *Ki T*/+ +, but no conclusions concerning a possible position effect can be drawn from the data in hand, since all *Ki T* animals are descended from a single exceptional animal, whose tailless phenotype may have been due to other factors by which he differed from his *Ki* +/+ *T* ancestors. For the present, taillessness in *Ki T*/+ + may be assumed to be an extreme effect of *Ki* or of *T* when combined with other unknown factors.

The other tailless offspring from *Ki* +/+ *T* × ++ did not survive long enough to be tested. It is not known whether they were crossovers or extreme variants of *Ki*/+ or *T*/+.

FREQUENCY OF CROSSING OVER BETWEEN *Ki* AND *T*

From crosses of *Ki* +/+ *T* by ++ the frequency of crossing over was found to be about 3.6–4.3 percent. It is now possible to measure crossing over from *Ki T*/+ + ♂ by crossing with l^0/l^1 ♀. Crossing over does not occur between l^0 and l^1 in females (l^0/l^1 males are sterile). Hence the two regular (non-cross-

over) types from the above cross will be *Ki T*/t^0 or *Ki T*/t^1 (tailless) and ++/+t^0 or ++/+t^1 (normal), while one class of crossover (*Ki* +/t^0 or *Ki* +/t^1 can be readily detected as Kink-tailed, since *Ki* and t^0 do not interact. Another class of crossovers + *T*/+ t^0 or + *T*/+ t^1 is tailless and indistinguishable from a non-crossover class. Thus the Kink-tailed animals from this cross will represent half the crossovers.

The results of such crosses are shown in the last columns of table 6. About equal numbers of normal (194) and tailless (181) were produced, together with nine or 2.4 percent Kink-tailed. Three of the latter (♂ 9714, ♀ 10505, ♀ 10568) were tested by t^0/t^1 or +/t^0 and produced no tailless animals, hence lacked *T* and were thus crossovers + *Ki*/t^0 or + *Ki*/t^1. The detected crossovers represent half of the total, which may thus be estimated as 4.8 percent. This is probably an overestimate because one of the non-crossover classes (*Ki T*/t^n) has poorer viability than either crossover class *Ki*/t^n or *T*/t^n. It is somewhat higher than the 3.6–4.3 percent found for *Ki* +/+ *T*, but the difference is not significant.

RECOMBINATION FROM *Fu* +/+ *Ki*

It was shown in our first report that *Fu* and *Ki*, in spite of their great phenotypic similarity, were not mutations at the same locus, since at least one case of crossing over between *Fu* and *Ki* was found. Several other recombination individuals have now been tested and indicate that *Ki* and *Fu* are several crossover units apart.

The pertinent data are given in table 7. The normal offspring, which are

TABLE 7

Tests of recombination in crosses of Fu+/+Ki×++.

Fu+/+*Ki* PARENT	*Fu* OR *Ki*	TAILLESS	PROGENY NORMAL			TOTAL NORMAL	CROSSOVERS	TOTAL
			TESTED *Fu* OR *Ki*	TESTED ++	NOT TESTED			
♂♂(L)*	176		8		1	9	—	185
♀♀(L)*	229	1	18	5	15	38	5	268
♂♂(C)†	25	—				—	—	25
♀♀(C)†	25	—	2			2	—	27
	455	1	28	5	16	49	5	505

* At Lafayette.
† At Columbia.

classed as ++ (recombinations), gave the following progenies when tested by normal mates: (a) 74 normals, (b) 62 normals, (c) 61 normals and one doubtful, (d) 54 normal and one doubtful (the doubtful cases having abnormal tail tips possibly from injury), and (e) 112 normals to three clearly ab-

normal. In evaluating these results, it must be mentioned that animals with slight tail abnormalities resembling Fused or Kink are found occasionally in the Bagg albino strain used in the test crosses. The three abnormals from animal (d) are possibly of this type, or they may represent the effects of other genetic factors. It seems unlikely that the exceptions are due to the presence of *Fu* or *Ki* in the test animals which produced a total of 289 normal and five abnormal or doubtful offspring. Probably the five animals tested (a–d) were valid recombinations. If so they represent .99 ± .44 of the total progeny 505 from *Fu/Ki* × ++. Since only half of the crossovers could be detected by the methods used, this would indicate a minimum crossing over value of 1.98 ± .62 percent.

We have tried to increase the data and to remove the ambiguity due to the occurrence of doubtful and abnormal young in the test crosses. Several attempts have failed because of the poor viability of *Fu/Ki* animals. In one experiment, all ten offspring of a cross of *Fu/Fu* × *Ki*/+ proved to be *Fu*/+. Where viable, *Fu/Ki* animals have usually shown poor fertility. For these reasons a reliable crossover value for the *Fu-Ki* interval has not been obtained.

THE ORDER OF THE LOCI *Ki*, *T*, *Fu*

To determine the relative locations of *Ki*, *T*, and *Fu*, matings were made between *Fu Fu* and *Ki T*/+ +. The offspring should consist of *Fu*/+ and *Fu/Ki T* in equal numbers. Actually there appeared seven normal-tailed, 32 Fused or Kink-tailed, and 12 tailless, two of the latter showing the abnormal urogenital syndrome. Twenty-four of these were tested by crossing with normal-tailed males and were found to be distributed as follows:

Tested	*Fu*/+	*Fu/Ki T*
5 normal	5	—
17 Fused	15	2
2 tailless	—	2

Most of those tested proved to be *Fu*/+; only four were *Fu/Ki T*. All except two of the tailless F_1's died before they could be tested. It is probable that they contained more of the *Ki T/Fu* type which apparently is less viable than *Fu*/+.

The *Ki T/Fu* animals were tested by normal. They gave 167 offspring with abnormal tails (*Fu*, *Ki*, or tailless) and 18 with normal tails. The latter are either +/+ crossovers or *Fu*/+ (overlaps). To separate these latter genotypes, the normal exceptions were tested individually by normal-tailed mates. Of nine thoroughly tested, six gave only normal offspring and were classed as crossovers, while three gave some *Fu* offspring and were thus *Fu*/+.

To account for these crossovers, it must probably be assumed that *Fu* does not lie between *Ki* and *T*, for if it did, all six crossovers (the only ones detected) could have arisen only by double crossing over. It is much more likely that they are single crossovers and that the loci occur in one of the following orders: (a) *Ki T Fu*, (b) *Fu Ki T*.

If the order is *Ki T Fu*, then the +++ progeny would represent half the crossovers between *T* and *Fu*, and the frequency of these, 3.24 percent, is somewhat higher than the proportion found in the offspring of *Fu* +/+ *T*, which is 2.13 percent, and thus might favor the order *Fu* – *Ki* – *T*. The present evidence, however, does not distinguish between the two possible orders. The linkage summaries based on detected crossovers only (half of those occurring) show that the "half intervals" *Ki* – *T* (1.91 ± .30) and *Fu* – *T* (1.81 ± .48) are about the same. The *Fu* – *T* estimate would probably be increased by the discovery of additional crossovers among the 19 untested exceptions, and *Ki* – *T* would be increased by a lesser amount from the nine untested exceptions, probably leaving the two not significantly different. *Fu* – *Ki* appears to be shorter (.99 ± .44), although its difference from the above is not statistically significant, and the estimate may be too low by reason of the 16 untested exceptions. If *Fu* – *Ki* could be shown to be significantly less than *Fu* – *T*, the order *Fu* – *Ki* – *T* would be indicated. As it is, no interval can be said to represent the sum of two component intervals.

TABLE 8

Summary of linkage data for Fu, Ki, and T.

COMBINATIONS TESTED	TOTAL PROGENY	TESTED++ CROSSOVERS	UNTESTED EXCEPTIONS	PERCENTAGE CROSSOVERS DETECTED	
Fu+/*T* ♂♂	657	14	3	2.13	1.81 ± .48
Fu+/+*T* ♀♀	137	—	16	0. —	
Ki+/+*T* ♂♂	1128	14	4	1.24 ± .33	1.91 ± .30
Ki+/+*T* ♀♀	542	16	5	2.95 ± .73	
Ki T/++♂♂	395	9	—	2.28 ± .75	
Fu+/+*Ki* ♂♂	209	—	1	0. —	.99 ± .44
Fu+/+*Ki* ♀♀	296	5	15	1.69	
Ki T/*Fu* ♂♂	185	6	9	3.41 ± 1.37	
Totals	3549	64	53	1.80 ± .22	

There are several reasons why the present data are not competent to answer questions depending on the accurate measurement of crossing over and why adequate data will be hard to get. First, in matings involving phenotypically indistinguishable dominants, the best that can be hoped is that one of the two crossover classes, that containing neither dominant, will be detected. Secondly, this class often resembles phenotypically one of the non-crossover classes when one of the latter fails to manifest the dominant effect. Crossovers can theoretically be separated from "overlaps" by progeny-testing, but some exceptions are always lost and remain unknown. Third, the viability and fertility of animals with one, two, or three such dominants are unequal and variable. Under these conditions it is not considered feasible to obtain an accurate map of this area.

The summary in table 8, however, shows one conclusive result of great im-

portance. This is that crossing over does occur regularly and frequently within each interval of the *Ki–T–Fu* area. In some 3500 observations from heterozygotes containing two or three different mutations, a minimum of two percent of all offspring were shown to have arisen from crossing over within the area.

ABSENCE OF RECOMBINATION FROM *Ki* +/+ t^0

Since *Ki* and *T* have been shown to be at separate loci, while *T* has shown no recombination with either t^1 or t^0, it is important to test whether any recombination occurs between *Ki* and t^0 or t^1. The simplest test is to make matings $Ki/t^1 \times Ki/t^1$ and $Ki/t^0 \times Ki/t^0$. Since *Ki*, t^0, and t^1 all act as early lethals, such matings should "balance," if no recombination occurs, the only surviving offspring being Ki/t^1 and Ki/t^0, respectively, whereas, if recombination occurs, exceptional gametes *Ki* t^0 and ++ should be formed. The latter when uniting with a regular gamete t^0 would produce a normal-tailed exception, so that half of the crossovers should be detectable. All exceptions must of course be progeny-tested in order to separate overlaps (normal-tailed animals in which *Ki* is present but unexpressed) from crossovers.

In order to produce animals for the tests, the Kink progeny from the cross $Ki/+ \times +/t^1$ were tested by mating with Brachy ($T/+$). Progeny which were $Ki/+$ produced no tailless offspring and were rejected; while those which produced normal, Kink, and tailless offspring were assumed to be *Ki* +/+ t^1. Similar crosses produced *Ki* +/+ t^0.

Table 9 gives the results of the testing of those Kink animals which produced tailless when bred to Brachy. The females in each case gave the ratios expected from the cross $Ki/t^1 \times T/+$—that is, one-quarter normal ($+/t^1$) one-half Kink tail ($Ki/+$, Ki/T); one-quarter tailless (T/t^1); the males in all cases gave too many offspring in those classes receiving t^1 from the father,—that is, normal ($+/t^1$) and tailless (T/t^1). This has been shown to occur wherever t^1 or t^0 is transmitted by males and occurs similarly in combinations of *Ki* with t^1 and t^0. Those animals shown by test to be *Ki* +/+ t^1 or *Ki* +/+ t^0 could not be distinguished phenotypically from $Ki/+$—that is, neither t^1 or t^0 has any detectable modifying effect on *Ki*.

Those animals shown to be *Ki* +/+ t^1 were bred together; similarly *Ki* +/+ t^0 males were crossed with *Ki* +/+ t^0 females, and balanced lines of each were set up and maintained for several generations. The results are shown in table 10. Out of 279 offspring, all except four were typical Kinks. Of the four exceptions, only one could be tested. This proved to be Ki/t^0—that is, an overlap. These data provide no evidence of crossing over between *Ki* and t^1 or t^0. The lines were difficult to maintain, since litter size was small (due to the death of two classes of embryos: *Ki Ki* and t^0t^0 or t^1t^1), and many animals suffered from the defects caused by *Ki*—that is, waltzing or deafness.

ABSENCE OF RECOMBINATION BETWEEN *Fu* AND t^0 AND *Fu* AND t^1

Animals of the constitution *Fu* +/+ t^0 were produced by mating *Fu/Fu*

TABLE 9

Tests to detect Ki+/+t¹ and Ki+/+t⁰ animals.

BRACHY ♀ (T+)×Ki+/+t¹ ♂				BRACHY ♀×Ki+/+t⁰♂			
Ki/t¹ PARENT #	NORMAL	Ki	TAILLESS	Ki/t⁰ PARENT #	NORMAL	Ki	TAILLESS
♂7624	27	3	29	♂7973	18	11	24
7625	45	17	49	8081	30	42	22
7693	24	17	39	8159	45	26	49
8033	6	—	2	8433	3	—	3
8186	3	4	2	8537	10	9	7
8315	4	—	9				
Total	109	41	130	Total	106	88	105
Exp.	70	140	70	Exp.	75	149	75
Ki+/+t¹♂×BRACHY ♂ T+				Ki+/+t⁰♀×BRACHY ♂ T+			
♀7626	3	10	4	7970	5	8	2
7627	3	3	3	7971	5	7	4
7692	2	5	5	7972	6	6	2
8031	7	5	3		—	—	—
8032		4	3	Total	16	21	8
8038	2	4	3	Exp.	11	22	11
8087	2	3	4				
8088	7	9	2				
	—	—	—				
Total	26	43	27				
Exp.	24	48	24				

× +/t⁰. The *Fu* offspring were tested by *T*/+ and those which gave tailless progeny (*T*/t⁰) were selected and bred *inter se*. Similar experiments were carried out with t¹. Similar results were obtained with both experiments, and the results are combined in both discussion and tables.

The phenotypes *Fu* +/+ t⁰ and *Fu* +/+ t¹ are indistinguishable from each other or from *Fu*/+. Neither t⁰ nor t¹ acts as a strong modifier of *Fu*.

TABLE 10

Results of breeding "balanced" lines.
Ki+/+t¹ and Ki+/+t⁰

PARENTS	OFFSPRING		AVERAGE LITTER SIZE	RESULTS OF PROGENY TESTS
	KINK	NORMAL		
Ki/t⁰×Ki/t⁰	107	2	3·3	1 n=Ki/t⁰
Ki/t¹×Ki/t¹	172	2	3·6	

The results of the *inter-se* crosses of *Fu* +/+ t^0 × *Fu* +/+ t^0 (and of *Fu* +/+ t^1 × *Fu* +/+ t^1) are shown in table 11.

All except 36 of the progeny showed *Fu*. The normal-tailed exceptions may be either *Fu*/t^0 which fail to manifest *Fu*, or may arise from ++ recombination gametes—that is + +/+ t^0. To distinguish between these alternatives, 21 of the exceptions (12 ♂♂ 9 ♀♀) were tested by mating with *T*/+ (Brachy) and with normal (+ +). By normal mates, each exception produced *Fu* progeny, proving that an unexpressed *Fu* was present; by Brachy, each animal so tested produced tailless progeny (together with *Fu* and normal) indicating the presence of t^0 (or t^1) in the exceptional parent. All exceptions tested were thus shown to be *Fu* +/+ t^0—that is, they were normal overlaps and not recombinations.

TABLE 11

Results of matings of Fu+/+t^0×Fu+/+t^0 and Fu+/+t^1×Fu+/+t^1.

PARENTS	FU	TAILLESS	OFFSPRING NORMAL TAIL			TOTAL OFFSPRING	LITTER SIZE
			Tested *Fu*/t^0	Untested	Total exceptions		
Fu×*Fu*	472*	7	21	15	36	515	3.81

* Fourteen of these were recorded as normal-tailed at birth but as Fused at weaning.

It was necessary to progeny-test those *Fu* offspring of *Fu*/t^0 × *Fu*/t^0 matings which were to be used in further matings of *Fu*/t^0 × *Fu*/t^0 in order to eliminate the expected genotype *Fu Fu*. Out of 52 *Fu* tested by *T*/+ (Brachy), 44 proved to be *Fu*/t^0, and these only were used in further breeding; four proved to be *Fu Fu*, while in four cases the test was inconclusive. The number of *Fu Fu* detected is far below the expected proportion of one-third of the *Fu* offspring. There is other evidence that this is due to low viability of *Fu* homozygotes. Thus the litters from *Fu*/t^0 × *Fu*/t^0 were small (average 3.8), and abnormal animals were often found among the young at birth. One series of litters (from ♂ 10014) subjected to close scrutiny and dissection yielded four abnormals with imperforate anus, urethra or both, and four anaemics out of a total of 27 offspring dissected. Of the four homozygotes found, all had short abnormal tails. Of the seven tailless young from *Fu*/t^0 × *Fu*/t^0 none survived to be tested. The characteristics of *Fu* homozygotes will be discussed in another paper.

It may be concluded that no detectable recombinations of *Fu* with t^0 or t^1 have occurred in about 500 test progeny. Since only half of the crossover gametes (++) when combining with half of the non-crossovers (+ t^0) could be detected by the methods used, the test has only about 25 percent efficiency —that is, it contributes to the total tests of crossing over involving t^0 or t^1 about 125 negative observations.

EFFECT OF t^0 AND t^1 ON CROSSING OVER

The proof that crossing over occurs with some frequency in *Ki T*/+ + makes it possible to test whether t^0 and t^1 suppress crossing over in the interval *Ki*–*T*. Such tests can be made by mating *Ki T*/+ t^0 male or *Ki T*/+ t^1 male with t^0/t^1 females and comparing the results with those from *Ki T*/+ + × t^0/t^1.

Most of the tailless offspring from *Ki T*/+ + × t^0/t^1 may be expected to be *Ki T*/t^n, but a few of them may be + *T*/+ t^n (crossovers). In some cases another effect of *Ki* may be used to distinguish between these two genotypes. Many animals which carry *Ki* show the waltzing-deafness syndrome mentioned by CASPARI and DAVID (1940). From the tailless animals mentioned above, therefore, those may be assumed to be *Ki T*/t^n which show waltzing or which transmit it to their offspring. Ten tailless males met this test. Results obtained from these animals are shown in table 12.

TABLE 12

Tests of genotype and of recombination in Ki T/t^n *males.*

PARENTS		NORMAL	KINK	TAILLESS
MOTHER	FATHER			
normal (++)	*Ki T*/t^n*	175	54	12
normal (t^0t^1)	"	403	1?	432

* From *Ki T*/++×t^0t^1.

When crossed with normal females, such animals gave 175 normal and 66 Kink or tailless offspring. The excess of normal is due to the usual excess of t^n sperm formed by heterozygous males. The cross of *Ki T*/t^n males by t^0/t^1 females constitutes the crucial test. The expectation here is that non-crossovers will be *Ki T*/t^0 and *Ki T*/t^1 (tailless) and t^0/t^1 (normal-tailed), while one class of crossovers (*Ki* +/+ t^n) should be clearly detectable as Kink-tailed. The 836 offspring fell into the two non-crossover classes with one doubtful exception (table 12). About half were normal tailed (t^0/t^1) and half[3] were tailless (*Ki T*/t^n.

[3] The ratio in which these classes appear has little meaning, since it is known that *Ki T*/t^n males produce an excess of t^n sperm, and this should lead to an excess of normal-tailed progeny. The approximate ratio of *Ki T* to t^n sperm is given by the ratio of *Ki* to normal progeny in the cross *Ki T*/t^n × ++. This ratio was about 2.6 t^n:1 *Ki T* (175/66). From the cross *Ki T*/t^n×t^0t^1 we should thus expect offspring as follows:

SPERM	EGGS		TOTAL	EXPECTED		OBTAINED	
	t^0	t^1		NUMBER	PERCENTAGE	NUMBER	PERCENTAGE
1 *Ki T*	1 tailless	1 tailless	2 tailless	363.2	43.5	432	51.7
2.6 t^n	dies	2.6 normal	2.6 normal tail	471.8	56.5	403	48.3

The actual result shows a considerable deficiency of normal-tailed offspring. This is undoubtedly

The one possible exception was an animal with a slightly shortened tail, like a Brachy, T +. When tested by tailless (Tt^0), it gave three normal and two tailless as it would if it were t^0t^1. Although this test is not adequate, it is probable that this was a phenotypic variant of the type t^0t^1 and not a valid crossover.

We can conclude that in the presence of either t^0 or t^1 crossing over between *Ki* and T probably does not occur. This confirms the conclusion drawn from experiments with Ki/t^0, Ki/t^1, Fu/t^0, and Fu/t^1 and shows that t^0 and t^1 suppress crossing over in the whole region which includes the loci *Ki*, *Fu*, and T. Since this region is probably at least eight crossover units in length, t^0 and t^1 are revealed as effective over a considerable stretch of chromosome and therefore are not point or gene mutations. A summary of data on the absence of crossing over in the presence of t^0 or t^1 is given in table 13.

TABLE 13

Data showing suppression of crossing over by t^0 and t^1.

COMBINATION TESTED	TOTAL PROGENY	TESTED CROSSOVERS	UNTESTED EXCEPTIONS	PERCENTAGE CROSSOVERS
KiT/t^0 or $t^1 \times t^0t^1$	836	—	1	0.00
$Ki+/+t^n \times Ki+/+t^n$	279	—	3	0.00
$Fu+/+t^n \times Fu+/+t^n$	515	—	15	0.00
$T+/+t^n \times T+/+t^n$	4829	—	—	0.00
$t^0+/+t^1 \times T/+$	2488	—	—	0.00

There is no evidence as yet as to what kind of change in the chromosome t^0 and t^1 represent. If they are gross chromosome changes, it is more likely that they are inversions than deficiencies, since the compound t^0/t^1 is viable and since both t^0 and t^1 cover the lethal effect of *Ki* and T (Ki/t^0, Ki/t^1, T/t^0 and T/t^1 are viable). In the combinations studied each has a greater effect on T than on either *Ki* or *Fu* since T/t^0 and T/t^1 are usually tailless, while Ki/t^0, Ki/t^1, Fu/t^0, and Fu/t^1 resemble $Ki/+$ and $Fu/+$. It might thus be supposed that T showed exaggeration when opposite t^0 or t^1. Too much stress cannot be placed on this, however, since in outcross lines of T/t^0 and T/t^1, animals resembling $T/+$ have been found; while $T/+$, which usually has a short-tail, may in certain combinations be entirely tailless. These facts show that factors other than T, t^0 and t^1 are involved in producing the tailless phenotype; and until these have been made identical or comparable in all stocks, arguments from the interaction effects of t^0 and t^1 will have little weight.

due to the heavy mortality suffered by t^0t^1 animals both before and after birth (DUNN and GLUECKSOHN-SCHOENHEIMER 1943). Both variables, sperm ratio and selective mortality of t^0t^1 embryos, differ quantitatively in different matings. Several $Ki\ T/t^n$ males which were tested simultaneously by ++ and by t^0t^1 females regularly gave about 68 percent normal (+ t^n) to 32 percent *Ki T* offspring (actually 96:46) by ++ females and about 38 percent normal (t^0t^1) and 62 percent *Ki T* offspring by t^0t^1. With full viability of t^0t^1, the latter ratio should have been 51.5 percent normal. The deficiency of 13.5 percent represents the excess mortality of t^0t^1 over $Ki\ T/t^n$.

COMPARISON OF *Fu*, *Ki* AND *T*

As a result of the experiments described, we find that of the five mutations with similar effects, three (*Fu*, *T*, and *Ki*) are properties of distinct loci which can be readily separated by crossing over, while two (t^0 and t^1) are sectional changes which have not been separated or combined by crossing over. The question "how near together are the loci of these similar mutations" can thus refer only to the first three.

Because of difficulties in identifying recombination classes, only rough estimates of "distance" can be made. The most reliable is probably the interval *Ki–T*. Based only on progeny-tested exceptions, 39 crossovers in a total of 2065 offspring (with nine untested exceptions) were recognized, or 1.89 percent. If the nine untested exceptions were all crossovers, the maximum number would be 48 out of 2065 or 2.32. Since only one recombination class could be identified, the crossover percentage would be twice the percentage recognized, or from 3.78 (minimum) to 4.64 (maximum).

The *Fu* – *T* interval is similarly estimated to be about 4.26 to 5.16 percent. The data for *Fu–Ki* are the least numerous and reliable. The estimates for this interval vary from 1.98 to about twice this figure. The single crossovers detected in *Ki T* +/+ + *Fu* were probably in the *Fu*–*T* interval and do not increase our information on total distance. Although no single interval is equal to the sum of the remaining two, it is still likely that the maximum number of crossing over units between the most distant of the three loci is about eight, since individual intervals average about four or a little less.

DISCUSSION

The question to be asked therefore is: what is the likelihood that three similar mutations should occur by chance within an area of eight crossover units? To estimate this likelihood we need to know how many such loci there are in the mouse, and how many areas of eight crossover units. At present we have record of some ten loci at which have occurred mutations with effects on tail and axial skeleton similar to those of *Ki*, *T*, and *Fu*. The ten loci are: *T* (DUNN 1941); *Fu* (DUNN and CASPARI 1942); *Ki* (CASPARI and DAVID 1940); *Sd* (Short tail Danforth) (DUNN, GLUECKSOHN-SCHOENHEIMER, and BRYSON 1940); *st* (shaker short) (DUNN 1934); *sb* (stub) (DUNN and GLUECKSOHN-SCHOENHEIMER 1942); *tw* (twist) (DUNN and GLUECKSOHN-SCHOENHEIMER unpublished); *sc* (screw) (LAANES and MACDOWELL 1942); *fl* (flex) (HUNT et al. 1933); *pt* (pigtail) (CREW and AUERBACH 1941). If these loci are distributed at random among the 20 chromosomes of the mouse, the chance that any chromosome should have three of these loci is approximately $[(10!/3!7!)(1/20)^3(1-1/20)^7]20$. The chance for a group of four or more loci is negligibly small. We do not know the genetic lengths of mouse chromosomes, but if the average number of chiasmata is about two (CREW and KOLLER 1932), then the average map length per chromosome would be about 100, which would include about 12 segments of eight crossover units each. The chance that three similar loci should fall within one such segment is $(1/12)^2$; and the likelihood that all

three should fall in one chromosome and in one segment is the product of the above probabilities. This is about .001; or if we take the minimum length of the *Ki–Fu–T* areas as four crossover units, it is even less. In either case, it is highly improbable that the association is due to chance.

If these mutations are not distributed at random, then it is probable that their similarity is due to their nearness. There are three main ways in which such a condition might arise. All three mutations may represent replications or displacements of the same genetic material like the "repeats" discovered by BRIDGES (1935) in Drosophila; or partially overlapping deficiencies may have arisen in neighboring loci as MCCLINTOCK (1944) has found in maize; or an area of a chromosome may be differentiated in such a way that mutations occurring in it tend to affect the same parts of the body.

The only proved examples of mutations which owe their similarity to their derivation by replication of the same genic material are the cases of Bar and Double Bar (BRIDGES 1936; MULLER, PROKOFIEVA, and KOSSIKOV 1936) and the mimic mutations "Star" and "asteroid" in Drosophila (LEWIS 1945). Other possible cases of mimic mutations in Drosophila lying close to each other have been studied by GOTTSCHEWSKI (1936) and by OLIVER and GREEN (1944) in the case of mutations near the lozenge locus; while bithorax and bithoraxoid are so similar and so near (BRIDGES and BREHME 1944) that they, too, may represent mutations in repeated loci. In rabbits it may be significant that two phenotypically similar mutations Rex_1 and Rex_2 have been reported by CASTLE and NACHTSHEIM (1933) as closely linked.

The most complete cytogenetic analysis of such neighboring mimics is that described recently by LEWIS (1945) for the mutations at the Star and asteroid loci near the left end of the second chromosome of *D. melanogaster*. The analysis makes it highly probable that the mutations which have similar effects in making the compound eyes smaller and rougher than normal involve two loci, *S* and *ast*. These are separable by crossing over but are so close together that the map distance between them is of the order of 0.02 map unit. The two loci are located in the opposite halves of one chromosome element, which appears as a double band or doublet in the salivary gland chromosomes. The loci probably are repeats which had arisen from a single locus. Strong and characteristic position effects exist between the loci such that a mutant change at one of them, as *ast*, has a pronounced effect upon the manifestation of the other locus, such as *S*, depending upon whether the mutations are adjacent (*ast S*) or opposite (*ast*/*S*). LEWIS assumes that the position effect is due to the fact that the loci are repeats and extremely close together. He thus suggests that some groups of mutations which appear to act as multiple alleles may be resolved into adjacent repeated loci which, because of the common position effect, act as a developmental unit.

The series of mutations described in this paper might represent such a group of repeated loci. They were in fact originally regarded as allelic, and only when crossing over was proved to occur did it become evident that three loci were involved.

A repeat hypothesis applied to the present case would assume that an original locus $+^T$ may have been triplicated to become $+^T +^{T_1} +^{T_2}$. One locus may then have mutated to *T*, another to *Ki*, and a third to *Fu*. The mutations t^0 and t^1 which suppress crossing over in this area might be assumed to be rearrangements such as inversions involving these loci.

Since there is at present no cytological evidence of such repeated loci, this hypothesis cannot be decisively tested. However, three considerations make it improbable. In the first place, *T*, *Ki*, and *Fu* are probably not immediately adjacent, since a relatively large amount of crossing over occurs between each pair of loci. Second, both *Ki* and *T* act as early lethals—that is, the recessive lethal effect of *Ki* is not "covered" by the duplicated normal loci which are present. In our notation homozygous *Ki* would be $+^T Ki +^{T_2}/+^T Ki +^{T_2}$. If $+^T$ and $+^{T2}$ contain the same genetic material as $+^{T1}$ (that is, $+^{Ki}$), this should suffice for viability regardless of mutations at one of the duplicated loci. The third objection to the repeat hypothesis comes from our present knowledge of the developmental effects of *T*, *Ki*, and *Fu*. On the repeat hypothesis one should expect alterations in the duplicate loci to act in similar ways like the similar developmental effects of mutations at the same locus. Although evidence on this is not yet complete, unpublished observations of GLUECKSOHN-SCHOENHEIMER and DUNN make it highly probable that *Ki* and *T* differ markedly in their effects on early development.

As CHESLEY (1935) showed, *T* acts upon the development of the notochord and cells ancestral to it, *T T* embryos having no notochord; the effects of *T* on other axial structures are apparently due to the dependence of these other parts upon influences emanating from the notochord. In *Ki Ki* embryos, on the other hand, the notochord is probably normal, and the most important departure from normal is an over production of embryonic tissue which results in doubling of certain parts such as axis, heart and others. The similar phenotypes of *T* + and *Ki* + seem to be reached in different developmental ways. The effects of *Fu* are probably different from those of either *T* or *Ki*. It is also to be recalled that *T* has never been found to effect behavior or hearing, whereas both *Fu* and *Ki* do. There is thus less evidence of basic developmental similarity than we should expect if all three mutations arose from replicated loci.

The second possibility, that the five neighboring mutations may represent partially overlapping deficiencies, is suggested by the recent results of MCCLINTOCK (1944). Two recessive mutations affecting seedling color—namely, pale yellow (*pyd*) and white (*wd*)—were shown to be small deletions in adjacent segments such that *pyd/pyd* was pale yellow and inviable beyond the seedling stage, *wd/wd* was white and inviable, while *pyd/wd* was pale yellow rather than normal as expected, since in *wd* the material containing the normal allele of *pyd* has also been deleted. Another mutation, yellow green seedling yg^2 was found to be a property of the chromatin that was deleted in *wd*, since yg^2/pyd gave normal seedlings, whereas yg^2/wd gave yellow green. Two series of allelic relationships are thus established: I, green > *pyd* > *wd;* and II, green > yg^2 >

wd. One might expect *pyd* and *yg*^{2} to interact as alleles, but this combination gives normal green color. This situation resembles the relations of the two lethals l^0 and l^1 since l^0/l^1 may be normal; while T/l^0 and T/l^1, although viable, each produce a mutant phenotype, tailless, which may represent an exaggeration of the effect of T. One might thus think of T as a deficiency including the loci at which mutations to l^0 and l^1 have occurred—that is, l^0 and l^1 behave as "pseudo-allelic" to T, in the sense in which BRIDGES (MORGAN, BRIDGES, and SCHULTZ 1938) used the term. The effects of l^0 and l^1, however, are not confined to single loci, since they prevent crossing over in the whole area studied. *Ki* could be represented as a deficiency within the area covered by l^0 and l^1, and possibly *Fu* also, although since *Fu Fu* may be viable, it could not lack much genic material.

MCCLINTOCK has described the methods by which such allelic or pseudo-allelic "mutations" occur in maize as a result of chromosome breakage which repeatedly induces mutants with the same small deficiencies and the same phenotypic changes. A similar mechanism may have operated to produce the five mutations described in this paper.

However, there are marked differences between the mutations encountered in mice and those studied by MCCLINTOCK in maize. The maize mutations were all recessive, whereas three of the mouse mutants are dominant, hence the phenotype in the latter cannot be due to a homozygous deficiency. In mice, moreover, all of the dominants are separable by crossing over, and thus properties of *different* areas of chromatin. Even though the mechanism responsible for the origin of the maize mutations should also have produced the several changes in the mouse, we should still be left without an explanation as to why different neighboring blocks of chromatin should produce similar but not identical phenotypes. Nor is this relationship clear in MCCLINTOCK's case. Pale yellow and white phenotypes seem to be due to losses of specific loci in adjacent chromomeres, but there is no indication whether these properties are associated with adjacent chromomeres by chance or by some factor resulting from propinquity. The type of change (loss or reduction of chlorophyll) is so frequent in plants that it may be the common expression of a great variety of changes, any one of which might have a good chance of occurring in any block of chromatin. Such seedling mutations may well be the phenotype toward which many small deficiencies converge, and thus their resemblance may be unconnected with their proximity. For these reasons it is doubtful if analogy with the maize mutations can shed much light on the main question at issue—namely, the relationship between nearness in the chromosome and phenotypic resemblance.

The third hypothesis assumes that the area in which these mutations occurred is so constituted that mutative changes in it are likely to affect the axial skeleton and related structures. This is not to say that among the chromosomes of the mouse there is a "tail area" or a "spinal area" where genes regulating these parts are located. Such relationships between genes and development apparently do not exist as a rule and are made improbable in special

cases by the epigenetic nature of development and the dependence of part upon part and gene upon gene. But it is conceivable and examples exist that mutative changes of a certain type are always accompanied by the same type of developmental change. One of the earliest examples of this was the mutant change "Minute bristles" in *Drosophila melanogaster*. Many mimic or duplicate "Minute" mutations had this in common, that each was lethal when homozygous and each involved the deletion of a small section of chromosome. In addition all of the Minutes which were tested for effect on rate of development were found to delay the growth of the larvae and the onset of pupation (SCHULTZ 1929; DUNN and MOSSIGE 1937; BREHME 1939). The areas in which Minute mutations have been recorded are too numerous and too scattered to make it at all likely that one or a few repeated loci are responsible. It is more probable that deletion of a certain quantity of genic material so disturbs development at the time when bristles are being determined as to regularly cause this process to fall below some normal level and to result in small bristles. The numerous mutants in maize in which the amount of chlorophyll is reduced (albino, luteus, virescent and pale types generally) perhaps also represent a convergent response of many different small deficiencies which upset the chlorophyll-forming mechanism in similar ways.

However, amount of genic material deleted cannot be the sole determinant of such phenotypes as "Minutes" and chlorophyll deficient mutants, since the individual mutants differ among themselves. Whether these differences are correlated with the extent of deficiency (in the case of Minutes) is not known; but it is evident that the phenotype depends also upon the kind of genic material which is changed, since not all deficiencies are accompanied by Minute or by chlorophyll effects. The kind of change in the chromosome by which the mutation occurs may also be important in producing the convergence, but of this little is known.

In the present case the mutations *T*, *Ki* are lethal and *Fu* is sub-lethal; all are dominant and all converge on a similar phenotype in respect of tail form. It might be assumed then that the area of chromosome in which they and t^0 and t^1 occur is by its structure such that any mutation in it is likely to be so extensive that it will disturb development at the time when the form of the tail and spinal column is being determined. Tail abnormalities, on this view, would be common responses to developmental disturbances, just as "Minute" mutations seem to be; the response would be determined by the "size" of the mutation, and changes in the section of chromosome in question would be more likely to reach the required "size" by reason of structural peculiarities. The form-dependence ("organizer") relationships between the parts of the developing axial structures (notochord, spinal column and cord) and between these and other systems such as the urogenital system and the gut probabaly rest on easily disturbed equilibria, since correlated abnormalities in these parts are common both from genetic and non-genetic causes (DUNN and GLUECKSOHN-SCHOENHEIMER 1944). Thus the responsiveness of the developing parts is probably of equal importance with the susceptibility to change of some particular segment

of chromatin. Since we have no cytogenetic evidence of the type of change involved, this hypothesis has not been tested. Evidence concerning the developmental relations of the effects of the five mutants discussed above will be published later.

SUMMARY

In the house mouse five mutations have been studied which produce similar effects causing shortness or absence of the tail or fusion of neighboring vertebrae, as well as certain other effects.

Breeding experiments involving some 5000 test progeny have shown that all five mutations are located near together in the same chromosome. The three dominants, *T*, *Fu*, and *Ki*, are separated from each other by distances of from two to five crossover units and are contained within a chromosome segment having a maximum length of about eight units. Two recessives, t^0 and t^1, appear to be sectional changes, since they suppress crossing over throughout this segment.

Three possible explanations of the relation between the contiguity of these mutations in the chromosome and the similarities in their developmental effects are considered. The first, that contiguity is due to chance, is rejected since the probability that three such similar mutations should chance to occur within one chromosome segment of eight units is only about 0.00007.

It is likewise considered unlikely that they represent "repeats" of one original locus, as in the case of Star and asteroid mutations of Drosophila (LEWIS 1945), since they are not immediately adjacent, and the lethal effect of a mutation at one locus is not "covered" by the other unmutated loci. Similar reasons indicate that they are probably not partially overlapping deficiencies like the group of neighboring mutations in maize described by MCCLINTOCK (1944).

It is suggested that the segment of chromosome in which these mutations occurred is so constituted that any change in it is likely to be extensive and to cause abnormalities in early developmental processes, the effects of which converge on the axial structures (spinal cord, notochord, etc.) which have "organizer" relationships with each other and with earlier processes.

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SUMMARIES FROM FORTHCOMING PAPERS

GREEN, M. M. *A study in gene action using different dosages and alleles of vestigial in Drosophila melanogaster.*—Received July 25, 1945.—A study was made of the nature of the action of recessive vestigial as evidenced by the interaction of different dosages of *vg*, and of four of its alleles, with Minutes which prolong the duration of the third larval instar.

The frequency and degree of scalloping of the wings in flies *vg*/+ with *M*(*2*)*1*^{2}, *M*(*1*)*n* or *M*(*3*)*w* were greater than in the controls. The increased duration of the third larval instar associated with each Minute.

Addition of an extra *vg*, by the use of a small duplication, increased the frequency and degree of scalloping both in controls (*vg*/*vg*/+) and in those carrying *M*(*2*)*1*^{2} or *M*(*3*)*w*. One *vg* expressed itself in competition with two normal alleles (*vg*/+/+) when Minutes were in the genome. With either Minute, *vg*/*vg*/+ flies had the most scalloping, *vg*/+ the next, and *vg*/+/+ the least. The effect away from normalcy was proportionally greater with *M*(*3*)*w*, which prolongs the third larval instar more, than it was with *M*(*2*)*1*^{2}.

Four alleles of vestigial were tested in combination with *M*(*2*)*1*^{2} and *M*(*3*)*w*. The two whose homozygotes are more extreme than homozygous *vg* also showed a higher degree of scalloping than *vg*/+ when the heterozygotes were combined with the Minutes. The two lesser alleles produced scalloped wings in combination with Minutes only when these alleles were homozygous.

At a temperature of 30°C, *vg*/+ with either Minute had no higher frequency or degree of scalloping than did the controls.

Crowding tends to counteract the effect of the Minutes.

It is postulated that *vg* and the four alleles, *vg*^{nw}, *vg*^{No2}, *vg*^{ni}, and *vg*^{nG}, are antimorphic genes which act to prevent wing development—that is, the action is contrary to that of the normal allele. In *vg*/+, the vestigial effect is below threshold due to the slower rate of development associated with *vg*. This can be compensated for by prolonging the third larval instar with Minutes, or by adding an extra *vg* to the genome. The two alleles *vg*^{ni} and *vg*^{nG} have a rate so low that prolongation of the development in heterozygous individuals does not change their dominance; but prolongation does cause the homozygotes to have wings that are scalloped—that is, the resulting development is in a direction opposite to normalcy.

DUBININ, N. P. *On lethal mutations in natural populations.*—Received August 1, 1945.—The natural mutation rate for lethals was studied in 14087 second chromosomes of *Drosophila melanogaster* from the populations of Kutaisi, Simferopol, and Sochi. The mutation rates proved to be 0.33 ± 0.07, 0.44 ± 0.08, and 0.45 ± 0.10 percent, respectively. The mutation rates were studied in the natural genotype and under natural conditions, as well as in crosses with a laboratory strain in the Moscow laboratory. An analysis of 20 strains from

the populations suggested the existence of a tendency toward different mutation frequencies.

It may be regarded as established that mutation rates may be identical in populations living in different environments, differing in the size of the breeding part of the population, and in the relations of the degrees of isolation and migration. In 35,114 second chromosomes from Florida, Simferopol, Kutaisi, Sochi, Delizhan, Kashira, and Serpukhov 147 lethals have been obtained—that is, 0.42 ± 0.03 percent.

The problem of recessivity of lethals was studied in 148 lethals from Kakhetia, Sochi, and Kutaisi. In 106,436 individuals the viability of lethal heterozygotes was compared with that of heterozygotes for a chromosome without a lethal. All the lethals proved to be recessive.

The idea of the importance of the seasonal cycle in the course of genetic processes in populations was expressed by DUBININ and ROMASHOV in 1932. The number of lethals eliminated through homozygosis equals, at equilibrium, the number of lethals arising through mutation ($q^2 = u$). Experimental analysis of the relations between the mutation rates and the frequencies of homozygosis for lethals, however, has shown that the expected equilibrium does not obtain in natural populations. The frequencies of homozygosis for lethals are as follows: Gelendzhik 1933—0.019 per cent, Gelendzhik 1934—0.031 percent, Ufa —0.091 percent, Simferopol 1938—0.034 percent, Simferopol 1939—0.152 percent, Kutaisi—0.248 percent. The frequency of homozygosis for lethals is evidently much smaller than the mutation rate.

Concentrations of lethals and frequencies of homozygosis for lethals were studied for different parts of the seasonal cycle. For July, the mean concentration of lethals in ten populations was found to be 14.0 percent, for September (four populations)—25.1 per cent, for October (four populations)—26.1 percent, for November (one population)—38.3 percent. The frequencies of homozygosis are: July 0.025 percent, August 0.091 percent, October 0.093 percent, November 0.248 precent. This shows a gradual dwindling of the discrepancy between the mutation and the elimination rates hand in hand with the numerical expansion of the populations and their saturation with lethals. This discrepancy is due to the lethals being rapidly eliminated during some and accumulated during other parts of the seasonal cycle. The accumulation of the lethals during the expansion of the populations, however, may be too rapid to be accounted for solely by the mutation pressure.

About a half of the lethals found in the populations are represented by single heterozygotes, while the other half are found repeatedly; thus, for Gelendzhik the figures are 72 and 62, respectively, for Ufa 19 and 24, for Simferopol 83 and 121, for Kutaisi 44 and 44. Some of the lethals reach concentrations of 1, 2, and even 3.5 percent. On the other hand, crosses between lethals from different populations showed only 19 percent for repeated lethals. The frequency of homozygotes obtained in crosses between lethals from the same population is 0.239 percent, and in crosses between lethals from different populations 0.057 percent on the average. This shows that the populations are differentiated ow-

ing to automatic genetic processes and that the concentration of lethals in them does not reflect solely the mutation rates. Nevertheless, the 0.057 percent frequency of homozygosis for lethals obtained in crosses between most remote populations shows that the distribution of lethals is not accidental but is in part determined by the mutation pressures. This is confirmed by the fact that lethals found repeatedly in different populations show a tendency to have high concentrations within populations as well; these lethals arise at relatively mutable loci.

WRIGHT, SEWALL. *Isolation by distance under diverse systems of mating.*—Received August 3, 1945.—The properties of large, uniformly distributed populations depend on the system of mating and the effective population number (N) of the random breeding "neighborhoods." It is shown that with density, d, of breeding individuals and with standard deviation, σ, of the coordinates of location of parents at some phase of their life cycles relative to the corresponding phase of offspring, $N=2\sqrt{n}\sigma d$ if the population has an essentially one dimensional distribution (for example, shore line, river), and $N=4\pi\sigma^2 d$ if there is continuity over an extensive area. Random mating and equal parental dispersions are assumed here. If there is no dispersion along one parental line (for example, no dispersion of seed) but dispersion measured by variance, $2\sigma^2$ along the other lines (for example, of pollen), the formulae are the same.

The differentiation of mean gene frequencies among neighborhoods or larger areas, within still larger areas, is investigated in four cases. (1) Populations of hermaphrodites, derived from equally dispersed gametes derived at random from the neighborhood except for a specified tendency toward self fertilization. (2) Populations consisting of permanent pairs, derived by random mating from the neighborhood, except for a specified tendency toward brother-sister mating, with equal dispersion of the sexes. (3) Populations in which each individual is produced by a separate random mating from the neighborhood. The densities of the populations of the two sexes may differ in this case, but dispersion is assumed to be the same. (4) Populations of hermaphrodites, derived from union of ♀ gametes that are not dispersed to any appreciable extent with ♂ gametes derived at random from the neighborhood, except for a specified tendency toward self fertilization.

If the effective breeding population of neighborhoods is 200, there is a moderate amount of differentiation among large subgroups as well as among neighborhoods, within still larger groups inhabiting an indefinitely large area. There are only slight differences among the four cases. Even 100 percent self fertilization in case 1 or 100 percent brother-sister mating in case 2 increases differentiation only to a rather slight extent.

If the effective breeding population of neighborhoods is only 20, there is great differentiation among large subgroups as well as among neighborhoods. The amount of differentiation is considerably greater in case (2) than in case (1) or (4) and considerably greater in case (3) than in case (2).

It is noted that this differentiation, due to cumulative effects of accidents of sampling, may be expected in actual cases to be complicated by the effects of occasional long range dispersal, mutation, and selection, but that in combination with these it gives the foundation for much more significant evolutionary processes than those factors can provide separately.

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CORRIGENDA

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Page 139, three lines from bottom, for "S^v" read "S^R."
Page 152, 13 lines from bottom, for "*Df-S*" read "*Dp-S*."
Page 160, last line, and page 161, first line, should read "as a duplication for the *S* locus and a deficiency for the *ast* locus—that is, its composition may be written S^+S^+."
Page 161, line 3, for "ast^+ ast^+" read "S^+S^+."
Page 163, nine lines from bottom, for "$(+ast)^4(S+)$" read "$(+ast)$ $(S+)$."
Page 165, five lines from top, for "lz^r and lz^{pl}" read "lz^s and lz^p."
Page 352, table 2, second line, column 9, for "199" read "196".

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